

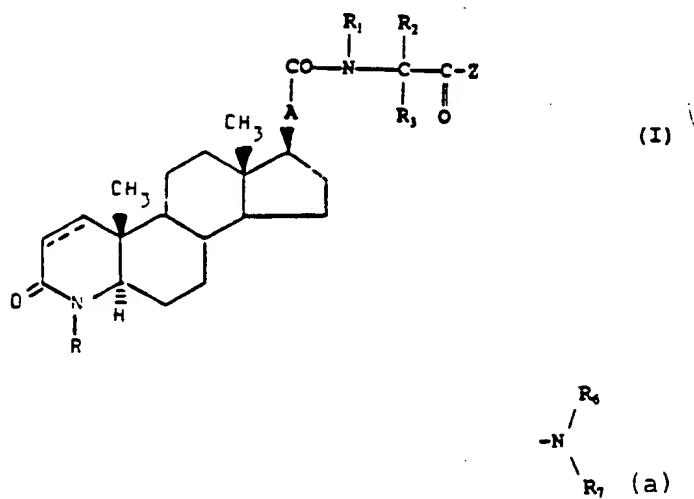
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07J 73/00, A61K 31/58		A1	(11) International Publication Number: WO 94/03476 (43) International Publication Date: 17 February 1994 (17.02.94)
(21) International Application Number: PCT/EP93/02038			(74) Agents: WOODS, Geoffrey, Corlett et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).
(22) International Filing Date: 29 July 1993 (29.07.93)			
(30) Priority data: 9216329.4 31 July 1992 (31.07.92) GB			(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(71) Applicant: FARMITALIA CARLO ERBA S.R.L. [IT/IT]; Via Carlo Imbonati, 24, I-20159 Milano (IT).			
(72) Inventors: PANZERI, Achille ; Via S. Francesco d'Assisi, 14, I-22055 Merate (IT). NESI, Marcella ; Via Mario Donati, 12, I-20100 Milano (IT). DI SALLE, Enrico ; Viale Andrea Doria, 5, I-20100 Milano (IT).			

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: 17 β -SUBSTITUTED 4-AZA-5 α -ANDROSTAN-3-ONE DERIVATIVES

(57) Abstract

A compound of formula (I), wherein R is a hydrogen atom or a C₁-C₄ alkyl group; A is a single bond or a straight or branched C₁-C₆ alkylene chain; R₁ is a hydrogen atom or a C₁-C₆ alkyl group; R₂ is a C₁-C₆ alkyl group, a C₅-C₇ cycloalkyl or a C₆-C₁₀ cycloalkylalkyl group, aryl or a C₇-C₁₀ arylalkyl group, or a C₆-C₁₀ heterocycloalkyl group; R₃ is hydrogen, a C₁-C₄ alkyl group or an aryl or a C₇-C₁₀ arylalkyl group; Z is a C₁-C₆ alkyl group, an -OR₅ group wherein R₅ is a C₁-C₆ alkyl group, a (a) group wherein each of R₆ and R₇ is hydrogen, C₁-C₆ alkyl, C₅-C₇ cycloalkyl, phenyl or R₆ and R₇ taken together with the nitrogen to which they are linked form a pentatomic or hexatomic saturated heteromonocyclic ring; and the symbol represents a single or a double bond, is a testosterone 5 α -reductase inhibitor and is therapeutically useful in benign prostatic hyperplasia, prostatic and breast cancers, seborrhoea, female hirsutism and male pattern baldness.

Best Available Copy

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TC	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

- 1 -

17 β -SUBSTITUTED 4-AZA-5 α -ANDROSTAN-3-ONE DERIVATIVES

The present invention relates to novel 17 β -substituted 4-aza-5 α -androstan-3-one derivatives, to a process for their preparation, and to pharmaceutical compositions containing them. These compounds are 5 compositions containing them. These compounds are inhibitors of androgen action, by means of testosterone 5 α -reductase inhibition.

In certain androgen responsive tissues the action of testosterone is mediated primarily through its 5 α -reduced 10 metabolite, dihydrotestosterone (DHT) (Bruchowsky N., Wilson J.D.; J. Biol. Chem. 243, 5953, 1968). The conversion of testosterone to dihydrotestosterone is catalysed by the enzyme 5 α -reductase and if 5 α -reductase is inhibited, the formation of dihydrotestosterone is reduced 15 and its specific androgenic effect is attenuated or prevented.

The 5 α -reductase inhibitors may find medical application for the treatment of hyperandrogenic conditions, e.g. certain prostatic diseases, such as benign 20 prostatic hyperplasia and prostatic cancer, and certain skin-hair conditions, such as acne, seborrhoea, female hirsutism and male pattern baldness (Siiteri P.K., Wilson J.D., J. Clin. Invest. 49, 1737, 1970; Price V.H., Arch. Dermatol. III, 1496, 1975; Sandberg A.A., Urology 17, 34, 25 1981). Also breast cancer treatment can take advantage from use of 5 α -reductase inhibitors as the said tumour is known to be aggravated by presence of androgens. Androst-

- 2 -

4-en-3-one-17 β -carboxylic acid and its methyl ester (Voigt and Hsia, *Endocrinology*, 92, 1216 (1973); Canadian Patent No. 970,692) are among the first steroidic compounds described as 5 α -reductase inhibitors.

5 Two 5,10-secosteroids having a 3-keto-4,5-diene system in the expanded ring have been found to be selective inhibitors of rat epididymal 5 α -reductase (Robaire et al., *J. Steroid Biochem.* 8, 307-310 (1977)).

10 The (20R)-4-diazo-21-hydroxy-20-methyl-5 α -pregnan-3-one and its analogs are reported to be enzyme activated inhibitors of testosterone 5 α -reductase (Blohm et al., *Biochem. Biophys. Res. Comm.* 95, 273-80 (1980); United States Patent 4,317,817).

15 Another series of enzyme-directed irreversible inhibitors of 5 α -reductase have been prepared by introducing a 6-methylene moiety into substrates type 3-keto- Δ^4 -progestins and androgens (Petrow et al., *Steroids* 38, 352-53 (1981); United States Patent 4,396,615)).

20 More recently unsaturated derivatives of 3-carboxy steroids have been reported as uncompetitive 5 α -reductase inhibitors versus testosterone (*Biorg. Chem.* 17, 372-376 (1989); Eur. Pat. Appln. no. 0289327).

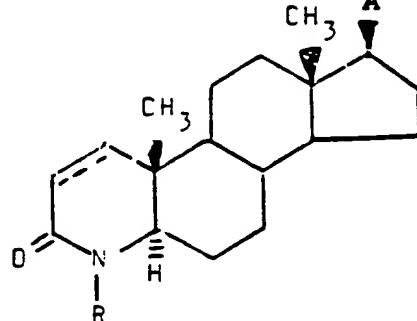
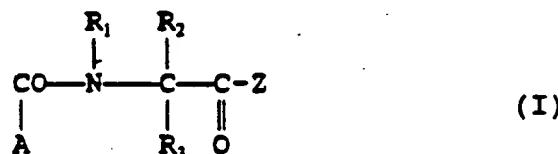
25 4-Aza steroids are by far the most studied steroid 5 α -reductase inhibitors. The compounds known in the art are reported in a very large number of publications and patents. In particular the 17 β -acylamides and their metabolites are described in: *J. Med. Chem.* 27, 1690-1701.

- 3 -

(1984), J. Med. Chem. 29, 2298-2315 (1986), Eur. Pat. Appln. No. 0004949; US patent No. 4,377,584; Eur. Pat. Appln. 0155096; US patent 4,845,104; Eur. Pat. Appln. 0462662; Eur. Pat. Appln. 0484094 A2; US Patent 4, 859,681; 5 WO 91/12261.

The invention provides compounds of the following formula (I)

10



wherein

15 R is a hydrogen atom or a C₁-C₄ alkyl group unsubstituted or substituted by one or more fluorine atoms;

A is a single bond or a straight or branched C₁-C₆ alkylene chain;

20 R₁ is a hydrogen atom or a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms;

R₂ is:

a) a C₁-C₆ alkyl group unsubstituted or substituted by one or more substituents chosen from fluoro, C₁-C₄ alkoxy carbonyl, carbamoyl, carboxy, hydroxy, C₁-C₄

- 4 -

alkoxy, amino, di- C_1 - C_4 alkylamino, mercapto and C_1 - C_4 alkylthio, or

5 b) a C_5 - C_7 cycloalkyl or a C_6 - C_{10} cycloalkylalkyl group, unsubstituted or substituted by one or more fluorine atoms, or

10 c) an aryl or a C_7 - C_{10} arylalkyl group, unsubstituted or ring substituted by one or more substituents chosen from halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, hydroxy and trifluoromethyl, or

15 d) a C_6 - C_{10} heterocycloalkyl group in which the heterocyclic ring contains one or more heteroatoms chosen from N, O and S, unsubstituted or ring substituted by one or more fluorine atoms;

15 R_3 is hydrogen, a C_1 - C_4 alkyl group or an aryl or a C_7 - C_{10} arylalkyl group, unsubstituted or ring substituted by one or more substituents chosen from halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, hydroxy and trifluoromethyl;

20 Z is:

20 a') a C_1 - C_6 alkyl group unsubstituted or substituted by one or more fluorine atoms,

25 b') an $-OR_3$ group wherein R_3 is a C_1 - C_6 alkyl group,

25 c') a $-N(R_6)(R_7)$ group wherein each of R_6 and R_7 , independently, is hydrogen, C_1 - C_6 alkyl, C_5 - C_7 cycloalkyl or phenyl or R_6 and R_7 taken together with the nitrogen to which they are linked form a pentatomic

- 5 -

or hexatomic saturated heteromonocyclic ring, optionally containing at least one additional heteroatom selected from oxygen and nitrogen; and

the symbol represents a single or a double bond;

5 provided that when Z is a group OR₂, R₂ is not an

unsubstituted C₁-C₆ alkyl group;

and the pharmaceutically acceptable salts thereof.

In the formulae of this specification the dotted line (.....) indicates a substituent in the α -configuration,

10 i.e. below the plane of the ring, and the wedged line (■) indicates a substituent in the β -configuration, i.e. above the plane of the ring. The configurations of the chiral centers in the side chain is unspecified; the invention is meant to include both the single "R" and "S" epimers as

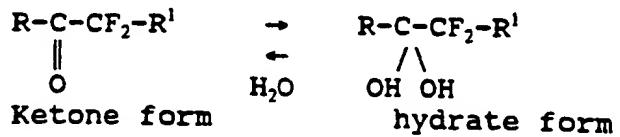
15 well as their "R,S" mixtures.

The invention includes the pharmaceutically acceptable salts of the compounds of formula (I) which contain a salifiable group.

It is known in the chemical literature that α -

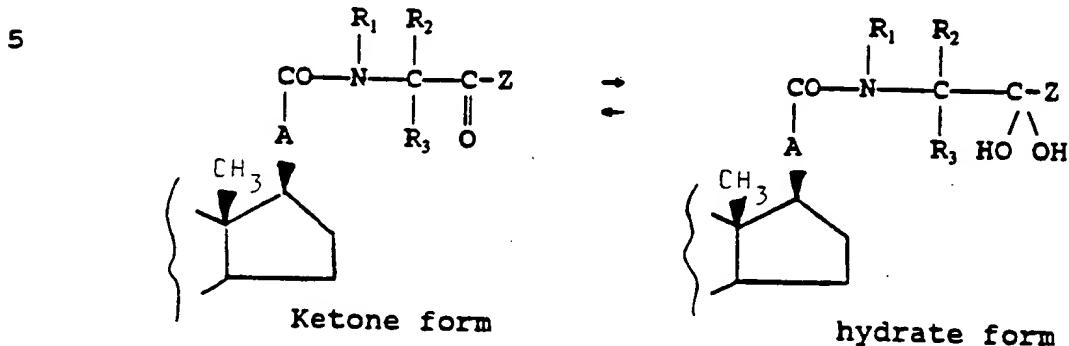
20 fluorinated ketones form stable gem-diols with water; so they are sometimes obtained as a mixture of a hydrate form and a ketone form, whose ratio depends on steric and electronic factors (Hudlicky M., Chemistry of Organic fluorine compounds, 2nd edition, Ellis Horwood Ltd.)

25



- 6 -

In this specification the α -fluorinated ketones are meant to include both these forms, i.e. they may exist in the pure ketone form or in the pure hydrate (gem-diol) form or as a mixture of both ketone and hydrate form.



The invention includes also all the possible isomers of formula (I) and their mixtures.

Also the metabolites and the metabolic precursors of the compounds of formula (I) are within the scope of the present invention.

In this specification the alkyl groups and the aliphatic portions of the arylalkyl, cycloalkylalkyl and the heterocyclic alkyl groups may be straight or branched chain.

15 A C₁-C₄ alkyl group may be, for example, methyl, ethyl, isopropyl, n-butyl or tert-butyl. The C₁-C₄ alkyl group may be unsubstituted or substituted by one or more preferably one, two or three, fluorine atoms and in particular may be difluoromethyl, fluoromethyl,
20 trifluoromethyl or 2,2,2-trifluoroethyl.

A C₁-C₆ straight or branched alkylene chain may be, for example, a straight or branched C₁-C₄ alkylene chain.

- 7 -

in particular, $\begin{array}{c} \text{CH}_3 & \text{CH}_3 \\ | & | \\ -\text{CH}- & -\text{CH}-\text{CH}_2-\text{CH}_2- \end{array}$, $-\text{CH}_2-$ or $-\text{CH}_2-\text{CH}_2-$.

A $\text{C}_1\text{-C}_6$ alkyl group may be, for example, methyl,

5 ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neopentyl, n-hexyl or isoheptyl. The $\text{C}_1\text{-C}_6$ alkyl group may be unsubstituted or substituted by one or more, preferably 1, 2, 3, 4, 5 or 6, fluorine atoms and may be, in particular, fluoromethyl,

10 difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, 1-trifluoromethylethyl, 2-trifluoromethylprop-1-yl, pentafluoroethyl, 1,1,1,3,3-hexafluoroprop-2-yl or 4,4,5,5,5-pentafluoropentyl.

15 A $\text{C}_1\text{-C}_4$ alkoxy carbonyl group may be, for example, methoxy-, ethoxy-, propoxy- or butoxycarbonyl, preferably methoxycarbonyl.

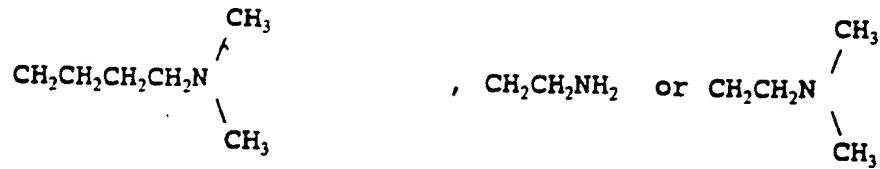
A $\text{C}_1\text{-C}_4$ alkoxy group may be, for example, methoxy, ethoxy, propoxy or butoxy, preferably methoxy.

20 A di- $(\text{C}_1\text{-C}_4\text{-alkyl})$ amino may be, for example, dimethylamino. A $\text{C}_1\text{-C}_4$ alkylthio group may be, for example, methylthio, ethylthio, propylthio, or butylthio, preferably methylthio or ethylthio.

A $\text{C}_1\text{-C}_6$ alkyl group wherein one or more hydrogen atoms

25 are substituted by one or more substituents other than fluorine may be, for example CH_2SH , $\text{CH}_2\text{SCH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{SCH}_3$, CH_2OH , CH_2OCH_3 , $\text{CH}(\text{OH})\text{CH}_3$, $\text{CH}(\text{OCH}_3)\text{CH}_3$, CH_2CONH_2 , $\text{CH}_2\text{CH}_2\text{CONH}_2$, CH_2COOH , $\text{CH}_2\text{CH}_2\text{COOH}$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$,

- 8 -



A C₅-C₇ cycloalkyl may be, for example, cyclopentyl, cyclohexyl or cycloheptyl.

A C₆-C₁₀ cycloalkylalkyl group may be, for example, a

5 (C₅-C₇ cycloalkyl) alkyl, preferably (C₅-C₇ cycloalkyl) methyl or (C₅-C₇ cycloalkyl) ethyl, in particular, cyclohexylmethyl, cyclohexylethyl, cyclopentylmethyl unsubstituted or substituted by one or more, preferably one, fluorine atoms, in particular, 1-fluoro-1-

10 cyclohexylmethyl.

An aryl group may be, for example, phenyl unsubstituted or substituted by one or more, preferably one, chloro, bromo, fluoro, C₁-C₄ alkyl, preferably methyl, C₁-C₄ alkoxy, preferably methoxy, hydroxy, or

15 trifluoromethyl groups, in particular, 4-methylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-trifluoromethylphenyl, 4-fluorophenyl.

A C₇-C₁₀ arylalkyl group may be, for example, phenyl (C₁-C₄ alkyl), preferably benzyl, unsubstituted or ring

20 substituted by one or more, preferably one or two, chloro, bromo, fluoro, C₁-C₄ alkoxy preferably methoxy, hydroxy or trifluoromethyl groups, in particular 4-hydroxybenzyl, 4-methoxybenzyl, 4-hydroxy-3-methoxybenzyl, 3,4-dimethoxybenzyl, 4-trifluoromethylbenzyl, 2-fluorobenzyl,

25 3-fluorobenzyl, 4-fluorobenzyl, 3-fluoro-4-hydroxybenzyl.

- 9 -

A C_6 - C_{10} heterocyclolalkyl group may be, for example, heterocyclo (C_1 - C_4 alkyl), for example heterocyclomethyl, preferably imidazolyl-methyl or indolylmethyl, unsubstituted or ring substituted by one or more, 5 preferably one, fluorine atoms, in particular, (4-imidazolyl)-methyl, (3-indolyl)-methyl, (5-fluoroindolyl)-methyl, (6-fluoroindolyl)methyl or (3-imidazolyl)methyl.

In the above formula (I) R is, preferably, hydrogen, methyl, ethyl, fluoromethyl, or 2,2,2-trifluoroethyl.

10 A is, preferably, a bond or $-\overset{\text{CH}_3}{\underset{|}{\text{CH}}}-$.
 R₁ is, preferably, hydrogen or methyl.
 R₂ is, preferably, the side-chain of the most common
 15 natural and unnatural amino acids, unsubstituted or substituted by one or more fluorine atoms.

When R₂ is an unsubstituted C_1 - C_6 alkyl group, it is preferably methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, 20 n-hexyl or iso-hexyl.

When R₂ is a substituted C_1 - C_6 alkyl group, it is preferably $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, CF_3-CH_2- , $\text{CF}_3-\text{CH}_2-\text{CH}_2-$,

$\text{CF}_3-\overset{\text{CF}_3}{\underset{|}{\text{CH}_2}}-\text{CH}_2-\text{CH}_2-$, $\text{CH}_3-\overset{\text{CF}_3}{\underset{|}{\text{CH}}}-$, $\text{CH}_3-\overset{\text{CF}_3}{\underset{|}{\text{CH}}}-\text{CH}_2$, $\text{CF}_3-\overset{\text{CF}_3}{\underset{|}{\text{CH}}}-$,
 $\text{CF}_3-\text{CF}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $\text{CH}_3\text{O}-\text{CH}_2-$ or $\text{CH}_3-\text{S}-\text{CH}_2-\text{CH}_2-$.

25 When R₂ is C_5 - C_7 cycloalkyl, it is preferably cyclohexyl.
 When R₂ is C_6 - C_{10} cycloalkylalkyl, it is preferably cyclohexylmethyl.

- 10 -

When R_2 is aryl, it is preferably phenyl or benzyl.

When R_2 is C_7-C_{10} arylalkyl, it is preferably benzyl.

When R_2 is heterocycloalkyl, it is preferably (3-imidazolyl)methyl or (3-indolyl)methyl.

5 R_3 is preferably hydrogen, methyl, ethyl, phenyl or benzyl.

When Z is C_1-C_6 alkyl as defined above under a'), it is preferably methyl, ethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, n-propyl, n-butyl or sec-butyl. When Z is a group OR, as defined above under b'), R_5

10 is preferably methyl, ethyl or t-butyl.

When Z is a group $\begin{array}{c} R_6 \\ | \\ -N \\ | \\ R_7 \end{array}$ as defined above under c')

it is preferably $-NH_2$, $-NHCH_3$, $-NHC_2H_5$, $-NHCH(CH_3)_2$, $-NHC(CH_3)_3$, $-NHCH_2C(CH_3)_3$, $-N(C_2H_5)_2$, $-N[CH(CH_3)_2]_2$, $-NH-\text{cyclohexyl}$, $NH-\text{Ph}$, piperidyl, piperazinyl or morpholino.

15 Pharmaceutically acceptable salts of the compounds of the invention include acid addition salts with inorganic, e.g. nitric, hydrochloric, hydrobromic, sulphuric,

perchloric and phosphoric, acids or organic, e.g. acetic, propionic, glycolic, lactic, oxalic, malonic, malic,

20 maleic, tartaric, citric, benzoic, cinnamic, mandelic and salicylic, acids, and salts with pharmaceutically acceptable bases, either inorganic bases, such as, for example, alkali metal, e.g., sodium or potassium, or

alkaline-earth metal, e.g., calcium or magnesium, or zinc 25 or aluminium hydroxides, or organic bases such as, for

- 11 -

instance, aliphatic amines as, e.g., methylamine, diethylamine, trimethylamine, ethylamine and heterocyclic amines, e.g., piperidine.

Preferred compounds of formula (I) are those wherein:

5 R is hydrogen or methyl;

A is a single bond;

R₁ is hydrogen;

R₂ is methyl, iso-propyl or iso-butyl, sec-butyl, tert-butyl, trifluoromethyl, 1-trifluoromethyleth-1-yl, 2-

10 trifluoromethylprop-1-yl, 2-methylthioeth-1-yl methoxymethyl, phenyl or benzyl;

R₃ is hydrogen or methyl;

Z is methyl, n-butyl, trifluoromethyl, pentafluoroethyl, a group OR₅ wherein R₅ is methyl, ethyl or tert-butyl; or a

15 group

$$\begin{array}{c} R_6 \\ | \\ -N \\ \backslash \\ R_7 \end{array}$$
 wherein each of R₆ and R₇ is, independently,

hydrogen, ethyl, isopropyl or neopentyl; and the symbol represents a single or a double bond provided that, when Z is a group OR₅ as defined hereinabove, R₂ is

20 trifluoromethyl, 1-trifluoromethyleth-1-yl, 2-

trifluoromethylprop-1-yl, 2-methylthioethyl, methoxymethyl, phenyl or benzyl.

Examples of specific compounds preferred under this invention are:

- 12 -

- 1) N-(1-neopentylcarbamoyl) 3-oxo-4-aza-5 α -androstan-17 β -carboxamide;
- 2) N-(1-neopentylcarbamoyl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;
- 3) N-[3-oxobut-2-yl] 3-oxo-4-aza-5 α -androstane-17 β -carboxamide;
- 4) N-[3-oxohept-2-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;
- 5) N-[1,1,1-trifluoro-2-oxobut-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;
- 10 6) N-[4-methyl-2-oxopent-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;
- 7) N-[1,1,1-trifluoro-4-methyl-2-oxopent-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;
- 8) N-[5-methyl-2-oxohex-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;
- 15 9) N-[4-methyl-2-oxohex-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;
- 10) N-[4,4-dimethyl-2-oxopent-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;
- 20 11) N-[1,1,1-trifluoro-3-oxobut-2-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;
- 12) N-[2,2,2-trifluoro-1-methoxycarbonyl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;
- 13) N-[5,5,5-trifluoro-4-methyl-2-oxopent-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;
- 25 14) N-[3,3,3-trifluoro-2-methyl-1-methoxycarbonylprop-1-

- 13 -

yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

15) N-[6,6,6-trifluoro-5-methyl-2-oxohex-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

16) N-[4,4,4-trifluoro-3-methyl-1-methoxycarbonyl-but-1-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

5 17) N-[5-methylthio-2-oxopent-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

18) N-[3-methylthio-1-methoxycarbonylprop-1-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

10 19) N-[4-methoxy-2-oxobut-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

20) N-[2-methoxy-1-methoxycarbonylth-1-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

21) N-[3-oxobut-2-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

15 22) N-[1,1,1-trifluoro-3-methyl-2-oxobut-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

23) N-[3-methyl-2-oxobut-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

20 24) N-[1,1,1-trifluoro-2-oxo-4-phenylbut-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

25) N-[1,1,1-trifluoro-2-oxo-3-phenylpropyl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

26) N-[1,1,1-trifluoro-3-methyl-2-oxo-3-phenylpropyl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

25 27) N-[1,1,1,2,2-pentafluoro-3-oxopent-4-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide.

- 14 -

compounds, according to their number, are tabulated below, with reference to the substituents as defined for formula (I):

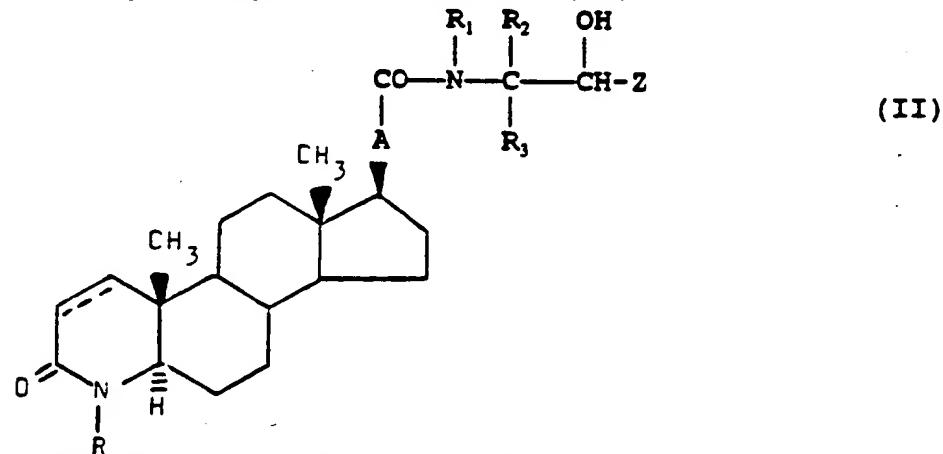
R	A	R ₁	R ₂	R ₃	Z
1) H	bond	H	CH ₃	H	NH(neopentyl)	single
2) H	bond	H	CH ₃	H	NH(neopentyl)	double
3) H	bond	H	CH ₃	H	CH ₃	single
4) H	bond	H	CH ₃	H	n-butyl	double
5) H	bond	H	CH ₃	H	CF ₃	double
6) H	bond	H	iso-propyl	H	CH ₃	double
7) H	bond	H	iso-propyl	H	CF ₃	double
8) H	bond	H	iso-butyl	H	CH ₃	double
9) H	bond	H	sec-butyl	H	CH ₃	double
10) H	bond	H	tert-butyl	H	CH ₃	double
11) H	bond	H	CF ₃	H	CH ₃	double
12) H	bond	H	CF ₃	H	OCH ₃	double
13) H	bond	H	CF ₃ CH ₃ -CH-	H	CH ₃	double
14) H	bond	H	CF ₃ CH ₃ -CH-	H	OCH ₃	double
15) H	bond	H	CF ₃ CHCH ₂ - CH ₃	H	CH ₃	double
16) H	bond	H	CF ₃ CHCH ₂ - CH ₃	H	OCH ₃	double
17) H	bond	H	CH ₃ -S-CH ₂ -CH ₂ -	H	CH ₃	double
18) H	bond	H	CH ₃ SCH ₂ -CH ₂	H	O-CH ₃	double
19) H	bond	H	CH ₃ -O-CH ₂	H	CH ₃	double

- 15 -

R	A	R ₁	R ₂	R ₃	Z
20) H	bond	H	CH ₃ -O-CH ₂	H	O-CH ₃	double
21) H	bond	H	CH ₃	H	CH ₃	double
22) H	bond	H	CH ₃	CH ₃	CF ₃	double
23) H	bond	H	CH ₃	CH ₃	CH ₃	double
24) H	bond	H	PhCH ₂	H	CF ₃	double
25) H	bond	H	Ph	H	CF ₃	double
26) H	bond	H	Ph	CH ₃	CF ₃	double
27) H	bond	H	CH ₃	H	CF ₂ CF ₃	double

The compounds of formula (I) may be obtained by a process comprising:

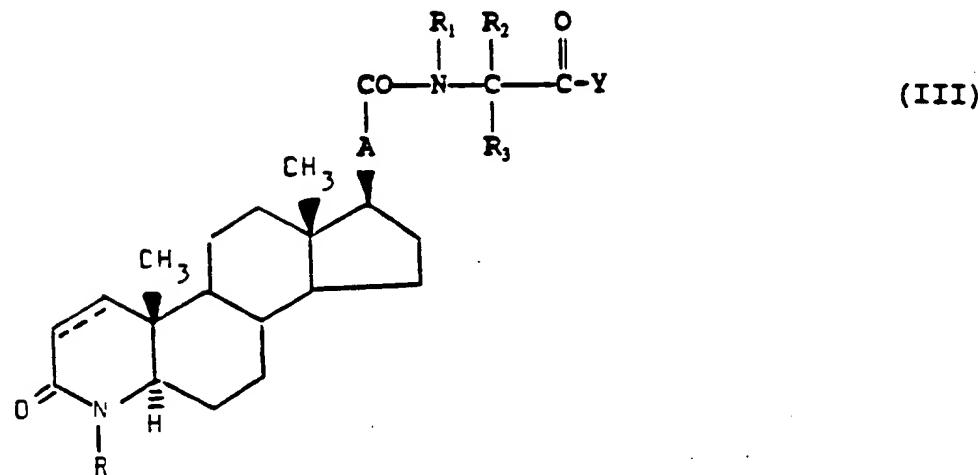
(1) oxidizing a compound of formula (II)



5 wherein R, R₁, R₂, R₃, A and the symbol are as defined above and Z is a C₁-C₆ alkyl group, unsubstituted or substituted by one of more fluorine atoms, so obtaining a compound of formula (I) wherein R, R₁, R₂, R₃, A and the symbol are as defined above and Z is a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms; or

- 16 -

(2) reacting a compound of formula (III)



wherein R, R₁, R₂, R₃, A and the symbol are as defined above and Y is OH or an activating group of the carboxy function with a compound of formula (IV)

5 the carboxy function with a compound of formula (IV)



wherein R_6 and R_7 are as defined above so obtaining a compound of formula (I) wherein R_1 , R_2 , R_3 , R_4 , R_5 , A and

10 group as defined above; or

the symbol are as defined above and z is a $-N$

group as defined above; or

(3) reacting a compound of formula (III) as defined above with a compound of formula (V)

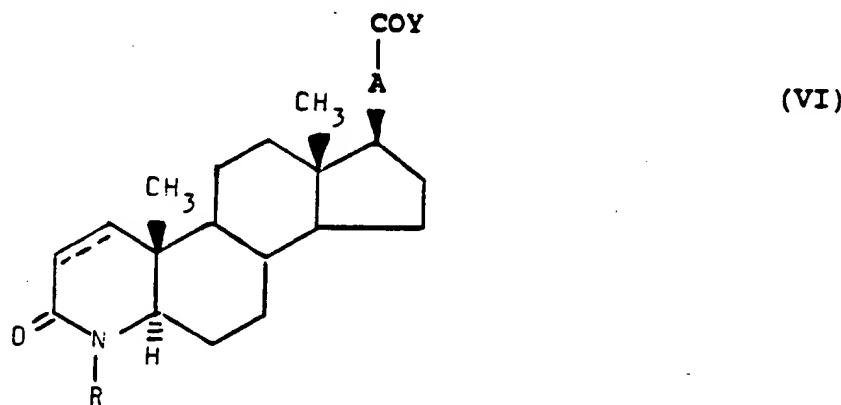


wherein R₃ is a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms and M is a metal atom or a metal-halogen group so obtaining a

- 17 -

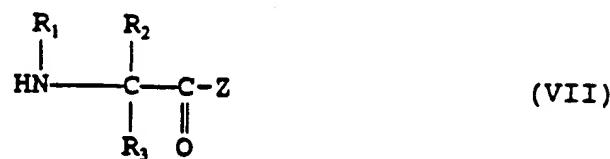
compound of formula (I) wherein R, R₁, R₂, R₃, A and the symbol are as defined above and Z is a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms; or

5 (4) reacting a compound of formula (VI)



wherein R, A and are as defined above and Y is OH or an activating group of the carboxy function with a compound of formula (VII)

10



wherein R₁, R₂, R₃ and Z are as defined above, so obtaining a compound of formula (I) wherein R, R₁, R₂, R₃, A, Z and the symbol are as defined above; and if desired,

15 (5) dehydrogenating a compound of formula (I) wherein R, R₁, R₂, R₃, A and Z are as defined above and the symbol is a single bond, so obtaining a corresponding compound of formula (I) wherein R, R₁, R₂, R₃, A and Z are as defined above and the symbol

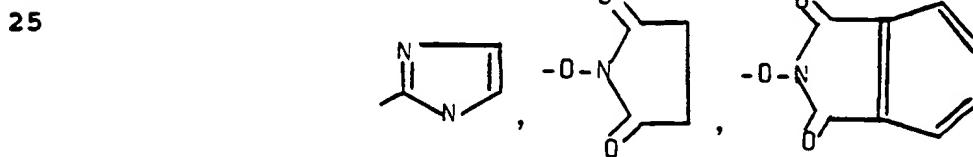
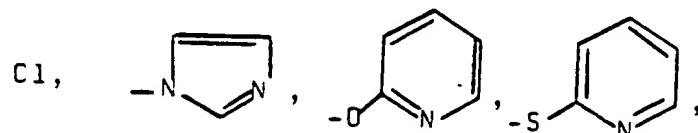
- 18 -

.... is a double bond, and, if desired, converting a compound of formula (I) into a pharmaceutically, acceptable salt thereof and/or if desired separating a mixture of isomers of formula (I) into the single 5 isomers.

The oxidation of a compound of formula (II), according to the process variant (1), may be carried out according to the Swern methodology, as described in Synthesis 1981, 165.

10 In particular, the oxidation may be carried out treating the compound dissolved in a solvent such as, for example, methylene chloride with dimethylsulphoxide and oxalyl chloride, at a temperature ranging from about -78°C to room temperature for a time varying from about 15 15 minutes to about 2 hours.

When Y is an activating group in the compound of formula (III) and (VI), it may be any suitable activating group of the carboxy function which is useful in the formation of amidic or peptidic linkages. It may be, for 20 instance, one of the following groups:



- 19 -

The reaction of a compound of formula (III) with a compound of formula (IV), according to the process variant (2), may be carried out in an inert solvent such as, for example, CH_2Cl_2 , THF, AcOEt, DMF, benzene or toluene, at a 5 temperature ranging from about 0°C to about 100°C, optionally in the presence of an organic base such as, for example, pyridine, p-dimethylamino-pyridine or triethylamine for a time varying from about one hour to about 24 hours.

10 In the compounds of formula (V) when M is a metal atom it is preferably Li and when it is a metal-halogen group is preferably MgCl , MgBr or MgI .

The reaction between a compound of formula (III) and a compound of formula (V), according to process variant 15 (3), may be carried out in an anhydrous solvent such as THF, Et_2O , dioxane, benzene under argon or nitrogen atmosphere at a temperature ranging from about -100°C to about the refluxing temperature of the solvent, for a time varying from about half an hour to about 24 hours.

20 A reaction between a compound of formula (VI) and a compound of formula (VII), according to the process variant (4), may be carried out, e.g., in an inert solvent such as, for example, CH_2Cl_2 , THF, AcOEt, DMF or benzene, at a temperature ranging from about 0°C to about 100°C, 25 optionally in the presence of an organic base such as, for example, pyridine, p-dimethylamino-pyridine or triethylamine, for a time varying from about one hour to

- 20 -

about 5 days.

The compounds of formula (VII) are often used as N-salt-derivatives, preferably hydrochlorides, hydrobromides or trifluoroacetates, and the free amino group is formed in situ in the presence of an organic base such as, for example, pyridine, or a tri-C₁-C₆-alkylamine, preferably triethylamine.

The dehydrogenation of a compound of formula (I) according to the process variant (5), may be carried out 10 with a dehydrogenating agent, e.g., benzeneseleninic anhydride or DDQ, in an anhydrous solvent such as, for example, chlorobenzene, dioxane, xylene, toluene, benzene, optionally in the presence of bis(trimethylsilyl)-trifluoroacetamide (BSTFA) (especially when DDQ is used), 15 at a temperature ranging from room temperature to the reflux temperature of the solvent, for a time varying from about two hours to 24 hours, preferably in an inert atmosphere of nitrogen.

Standard procedures may be used for separating a 20 mixture of isomers of formula (I) into single isomers.

The present invention also provides compounds of formula (II) wherein R, R₁, R₂, R₃, A and the symbol have all the same meanings as for the compounds of formula (I) and Z is a C₁-C₆ alkyl group unsubstituted or 25 substituted by one or more fluorine atoms, with the proviso that at least one of the groups, R, R₁, R₂, R₃ and Z contains at least one fluorine atom, and the

- 21 -

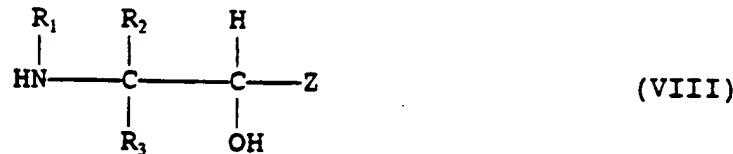
pharmaceutically acceptable salts thereof.

A preferred class of compounds of formula (II) according to the invention are the compounds of formula (II) wherein:

5 R is hydrogen or methyl;
 A is a single bond;
 R₁ is hydrogen;
 R₂ is methyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl, trifluoromethyl, 1-trifluoromethyleth-1-yl, 2-trifluoromethylprop-1-yl, 2-methylthioeth-1-yl,
 10 methoxymethyl, phenyl or benzyl;
 R₃ is hydrogen or methyl;
 Z is methyl, n-butyl, trifluoromethyl or pentafluoroethyl; and the symbol represents a single
 15 or a double bond provided that at least one of the groups R₂ and Z contains at least one fluorine atom.

A compound of formula (II) may be obtained by a process comprising:

(a) reacting a compound of formula (VI) wherein R,
 20 A, Y and the symbol are as defined above with a compound of formula (VIII)

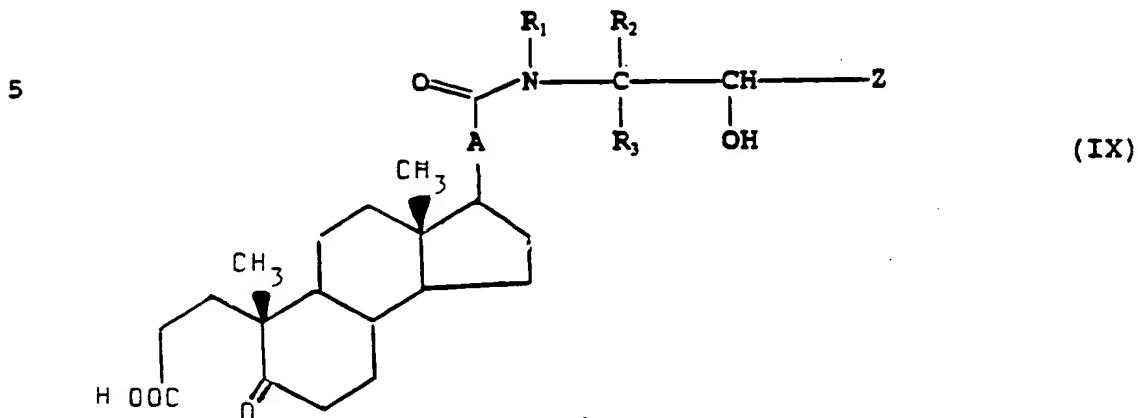


wherein R₁, R₂ and R₃ are as defined above and Z is a C₁-C₆ alkyl group unsubstituted or substituted by one or more
 25 fluorine atoms so obtaining a compound of formula (II)

- 22 -

wherein A, R, R₁, R₂, R₃ and the symbol are as defined above and Z is a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms; or

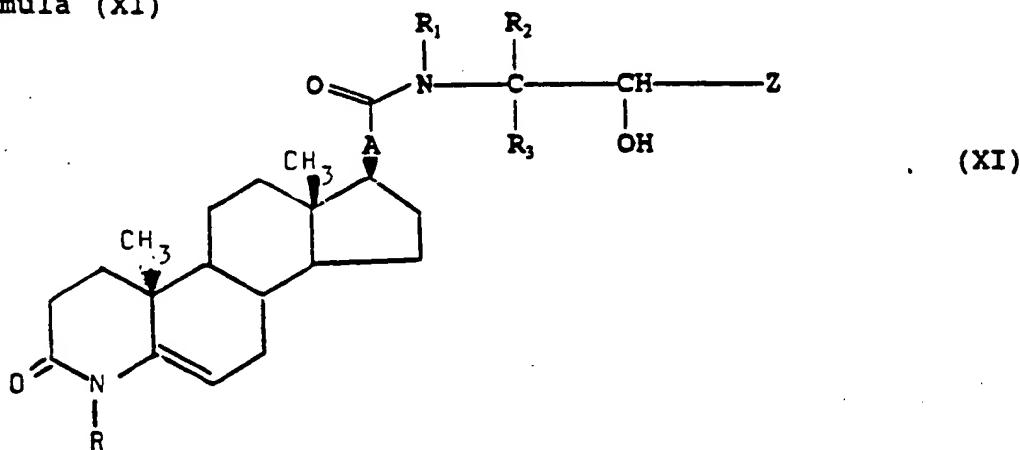
(b) reacting a compound of formula (IX)



wherein R₁, R₂, R₃ and A are as defined above and Z is a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms with an amine of formula (X)



10 wherein R is as defined above so obtaining a compound of formula (XI)



wherein A, R, R₁, R₂, and R₃ are as defined above and Z is a C₁-C₆ alkyl group unsubstituted or substituted by one or

- 23 -

more fluorine atoms, and hydrogenating the compound of formula (XI) so obtaining a compound of formula (II) wherein R, R₁, R₂, R₃ are as defined above, Z is a C₁-C₆ alkyl group unsubstituted or substituted by one or more 5 fluorine atoms and the symbol is a single bond.

The reaction of a compound of formula (VI) with a compound of formula (VIII), according to the process variant (a) may be carried out, for example in a solvent such as, for example, methylene chloride, ethyl acetate, 10 dimethylformamide or tetrahydrofuran, at a temperature ranging from about 0°C to 100°C, optionally in the presence of an organic base such as, for example, a C₁-C₆ trialkylamine, preferably triethylamine, for a time varying from 2 hours to about 5 days.

15 The compounds of formula (VIII) are often used as salt-derivatives, preferably hydrochlorides, and the amino group is formed *in situ* in the presence of an organic base such as, for example, a C₁-C₆-trialkylamine, preferably triethylamine.

20 The reaction of a compound of formula (IX) with a compound of formula (X), according to the process (b) may be carried out in an anhydrous organic solvent at a temperature from about 60°C to the reflux temperature of the solvent. It is suitably continued for a period of from 25 about 30 minutes to about four hours.

Preferably the solvent is ethylene glycol, dimethylformamide, dimethylsulphoxide, ethanol, methanol,

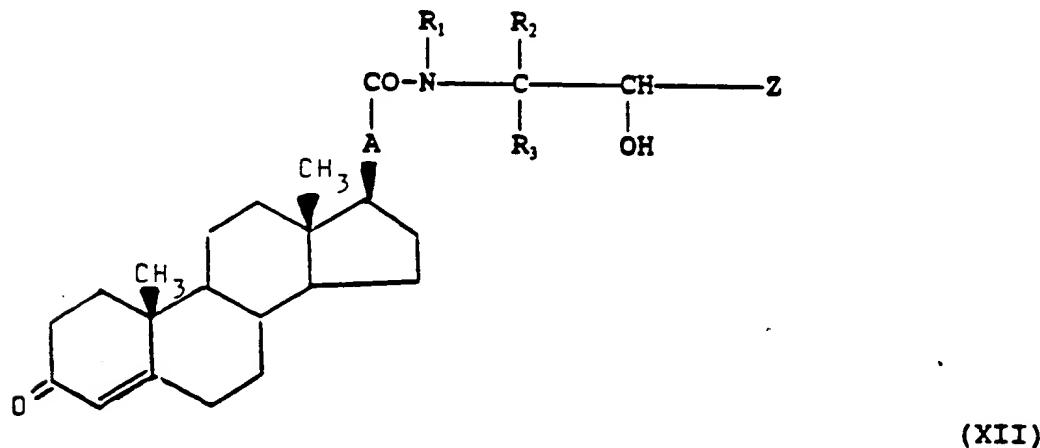
- 24 -

dioxane, ethylacetate or a mixture of any of these.

The hydrogenation of a compound of formula (XI) according to the process (b) may be carried out in an organic solvent under hydrogen pressure varying from about 5 1 atm to about 10 atm, in the presence of a hydrogenation catalyst. The temperature is typically from room temperature to about 100°C. The reduction time typically varies from about 30 minutes to about five hours.

Preferably the solvent is ethanol, acetic acid or a 10 mixture of any of these and the hydrogenation catalyst is platinum oxide (Adams' Catalyst), 5% or 10% palladium on charcoal or palladium hydroxide.

A compound of formula (IX) may be obtained by the oxidation of a compound of formula (XII)



15 wherein R₁, R₂, R₃ and A are as defined above and Z is a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms.

The oxidation of a compound of formula (XII) may be carried out, for example, in the presence of an oxidising

- 25 -

agent such as sodium metaperiodate and potassium permanganate in an organic solvent and a base such as aqueous potassium carbonate. It is suitably performed at a temperature of from room temperature to about 60°C, 5 typically for a period of from about one hour to about five hours.

Preferably the organic solvent is methanol, ethanol, acetone, tetrahydrofuran, dioxane, isopropanol, tert-butanol or a mixture of any of these.

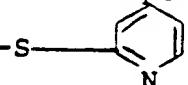
10 The reaction is suitably performed by adding a solution of the oxidising agent, for example, sodium metaperiodate and potassium permanganate, and the base such as potassium carbonate, in water to a solution of a compound of formula (XII) in an organic solvent, or by 15 adding simultaneously an aqueous solution of sodium metaperiodate and an aqueous solution of potassium permanganate to a solution of a compound of formula (XII) in an organic solvent and aqueous potassium carbonate.

Alternatively the oxidation of a compound of formula 20 (XII) may be carried out with ozone in an organic solvent. The reaction is typically continued until all the starting material is consumed. The temperature of the reaction is suitably from about -78°C to room temperature. An oxidizing agent is then added to the reaction mixture to 25 destroy the resulting ozonide. Preferably, the solvent is methylene chloride, ethylacetate, methanol or a mixture of any of these. The oxidising agent is preferably hydrogen

- 26 -

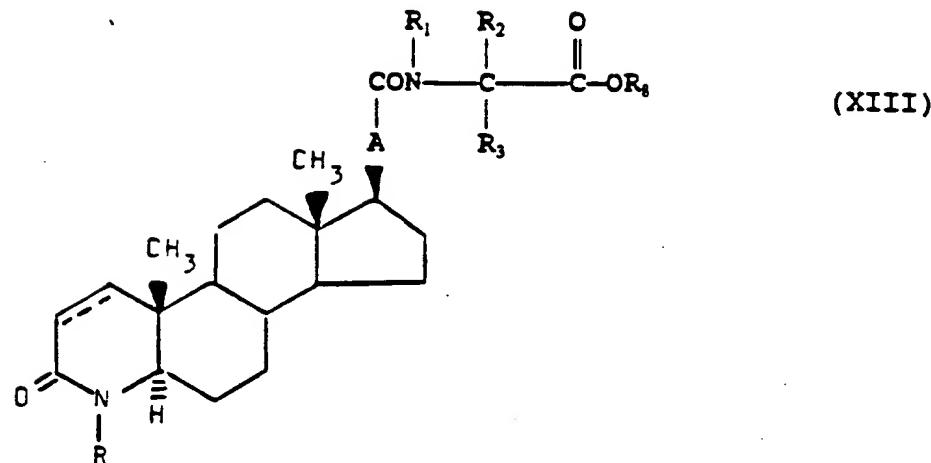
peroxide.

When the oxidation of a compound of formula (XII) is carried out with ozone, it is possible to perform the reaction of a compound of formula (IX) with an amine of 5 formula (X) as above described, by treating directly the ozonide containing reaction mixture with the amine of formula (X) typically in excess, thereby directly obtaining a compound of formula (XI).

A compound of formula (III) wherein Y is an 10 activating group of the carboxy function may be prepared reacting a compound of formula (III), wherein Y is an OH group with a suitable reagent, according to the methods used in the synthesis of amidic and peptidic linkages. For example, a compound of formula (III) wherein Y is 15  may be prepared treating a compound of formula (III), wherein Y is an OH group, with 2,2-dithio-dipyridine in the presence of triphenylphosphine in a solvent such as, for example, toluene or methylene chloride, at a 20 temperature ranging from 0°C to 40°C, for a time varying from half an hour to 8 hours.

A compound of formula (III) wherein Y is an OH group may be obtained hydrolysing a compound of formula (XIII)

- 27 -

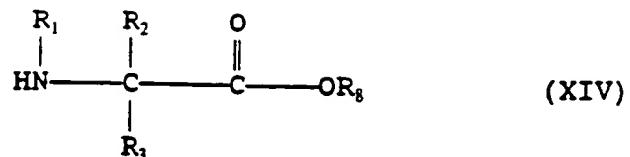


wherein R, R₁, R₂, R₃, A and the symbol are as defined above and R₄ is a protective group of the carboxy function easily hydrolysable in suitable conditions, such as, for 5 example, methyl, ethyl, tert-butyl, benzyl or 2,2,2-trihaloethyl.

The reaction may be carried out, for example, when R₄ is tert-butyl, in a solvent such as ethyl acetate, in the presence of a strong acid, e.g. gaseous hydrochloric acid, 10 trifluoroacetic acid, at a temperature ranging from about 0°C to about 40°C, for a time varying from about half an hour to about 24 hours.

A compound of formula (XIII) may be obtained by reacting a compound of formula (VI), wherein Y is 15 preferably an activating group of the carboxy function with a compound of formula (XIV)

- 28 -

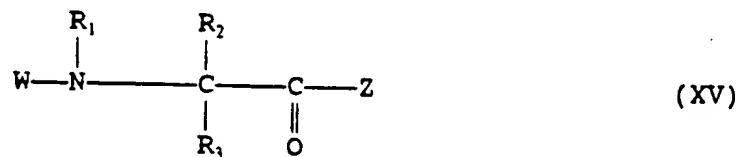


wherein R_1 , R_2 , R_3 and R_8 are as defined above.

The reaction may be carried out in a solvent such as, for example, methylene chloride, ethylacetate, benzene, 5 dioxane, chloroform, tetrahydrofuran, dimethylformamide or acetonitrile, for a time varying from about half an hour to about 72 hours, at a temperature ranging from about 0°C to the reflux temperature of the solvent (see, for example, *Tetr. Lett.* 22, 1901-904 (1970)).

10 The compounds of formula (VI) are known compounds (J.M.C. 29 (II) 2298-2315 (1986)).

A compound of formula (VII) may be obtained deprotecting a compound of formula (XV)



15 wherein R_1 , R_2 , R_3 and Z are as defined above and W is an amino protecting group commonly used in the synthesis of α -aminoacids and peptides, such as, for example, *N*-benzyloxycarbonyl (Cbz), *N*-tert-butoxycarbonyl (BOC), 2,2,2-trichloroethoxycarbonyl (TCloc), 2,2,2-20 tribromoethoxycarbonyl (Tbcoc), trifluoroacetyl (Tfac).

The reaction conditions for the deprotection depend on the amino protecting group used.

For example, when W is a BOC group, the reaction may

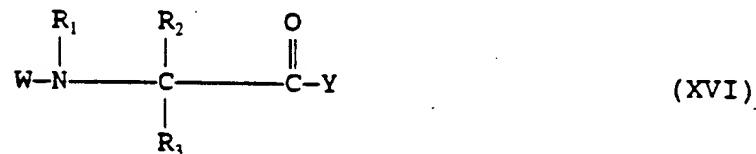
- 29 -

be carried out in a solvent such as, for example, methylene chloride, chloroform or ethyl acetate, in the presence of a strong acid, e.g. hydrochloric acid or trifluoroacetic acid, optionally in the presence of a tert-butyl cation 5 scavenger such as thioanisole, at a temperature from about 0°C to about 40°C, for a time varying from half an hour to 24 hours.

A compound of formula (XV) wherein R₁, R₂, R₃ and W

are as defined above and Z is a $\begin{array}{c} R_6 \\ | \\ -N \\ | \\ R_7 \end{array}$ group wherein R₆

10 and R₇ are as defined above, may be obtained reacting a compound of formula (XVI)



wherein R₁, R₂, R₃, W and Y are as defined above with a compound of formula (IV).

15 For example, when Y is S  the reaction may be carried out in a solvent such as methylene chloride, ethyl acetate or dimethylformamide, for a time varying from about half an hour to 24 hours, at a temperature ranging from about 0°C to the reflux temperature of the solvent.

20 The compounds of formula (XV) wherein R₁, R₂, R₃ and W are as defined above and Z is a C₁-C₆ alkyl group are known compounds; for example, they can be prepared starting from α -amino acids, according to the procedure reported in

- 30 -

J.O.C. 48, 2260-2266 (1983) or to the Dakin-West reaction (J. Biol. Chem. 78, 91, 1928).

The compounds of formula (XV), wherein R₁, R₂, R₃ and W are as defined above and Z is a C₁-C₆ alkyl group 5 unsubstituted or substituted by one or more fluorine atoms are known compounds or they can be obtained by known methods, for example, when Z is CF₃, the compounds are obtained as reported in Tetr. Lett. 27(2), 135-138 (1986) and Tetr. Lett. 27(14), 1579-1582 (1986).

10 The compounds of formula (IV), (V), (VIII), (X), (XII), (XIV) and (XV) wherein Z is a group OR₃ as defined above and the compounds of formula (XVI) are commercially available compounds or they may be prepared by known methods described in the literature.

15 The compounds of formulae (I) and (II) of the present invention inhibit specifically the testosterone 5 α -reductase enzyme and, therefore, are potent antiandrogens.

For example, the inhibitory effect of the compounds of the invention on 5 α -reductase was determined *in vitro* 20 and *in vivo* according to the procedure reported herebelow.

In vitro assay of 5 α -reductase inhibition

Inhibition of 5 α -reductase was evaluated using the particulate fraction from homogenates of hyperplastic human prostates as the enzyme source. The particulate fraction 25 was prepared centrifuging prostate homogenate at 140,000 x g. The resulting pellet, washed several times, was resuspended in buffer and stored at -80°C in aliquots

- 31 -

containing \approx 10 mg protein/ml.

The assay for 5 α -reductase was done in a final volume of 0.5 ml, in 40 mM TRIS-HCl buffer pH 5.5, containing 1 mM dithiothreitol, 5 mM NADPH, 1 μ M [14 C]testosterone, an

5 aliquot of the enzyme preparation and various concentrations of the inhibitors. After 30 min incubation at 37°C the reaction was terminated by addition of 2 ml cold diethyl ether and the organic phase was separated, evaporated under N₂, and resuspended in ethyl acetate.

10 Testosterone metabolites in this extract were separated in TLC on silica gel F 254 plates (Merck), using chloroform, acetone and n-hexane (2:1:2) as developing solvent system.

Radioactivity on the plate was scanned and analysed from quantitative plots printed by a TLC-analyzer (Berthold).

15 The fractional 5 α -reduction of testosterone was calculated by relating the 14 C-radioactivity in the 5 α -reduced metabolites (5 α -dihydrotestosterone, 3 α - and 3 β -androstaneadiols) regions to the total radioactivity in the testosterone and 5 α -reduced metabolites regions.

20 The concentration of each compound required to reduce control 5 α -reductase activity by 50% (IC₅₀) was determined by plotting % inhibition versus log of inhibitor concentration.

25 In vivo inhibition of 5 α -reductase

The standard test for the antiandrogenic effect in rats was used. Prepuberal 22-day-old male rats were

- 32 -

castrated via scrotal incision under light ether anaesthesia. On the seventh day after orchiectomy, androgen replacement was performed via subcutaneous implantation of 1 cm-long Silastic^R tube (Dow-Corning, 5 model No. 602-265) filled with a mixture of 25% testosterone and 75% cholesterol. The rats were then treated orally with the tested compounds (7 animals/group), once daily for 7 consecutive days. Twenty four hours after the last dose the rats were sacrificed and the ventral 10 prostate was removed and weighed. Control animals (testosterone controls) received the vehicle (0.5 ml/kg of 0.5% Methocel/0.4% Tween 80). One group of castrated rats was not implanted with testosterone (castrated controls).

The mean percentage of inhibition of the T-induced 15 hypertrophic response of the prostate was calculated according to the following formula:

$$\% \text{ inhibition} = 100 \times (W_{TC} - W_I) / (W_{TC} - W_{CC})$$

where W_{TC} , W_{CC} and W_I are the mean prostate weight of testosterone control, castrated control and inhibitor 20 treated group, respectively.

As an example, the results obtained with some representative compound of the invention identified by their numbers in the list previously given are shown in the following table:

- 33 -

TABLE 1

In vitro and in vivo inhibition of 5 α -reductase

Compound	In vitro inhibition IC ₅₀ (nM)	% Inhibition of prostate weight at 3mg/kg/day p.o.
5	16	58
7	8	54
22	14	50

From the results reported in this Table it is evident that the new compounds are very potent 5 α -reductase inhibitors, both *in vitro* and *in vivo*.

10 In view of the above indicated activity the compounds of the invention are therapeutically useful in the situations in which a decrease in androgen action, by means of 5 α -reductase inhibition, is desirable such as, for example, benign prostatic hyperplasia, prostatic and breast 15 cancers and certain skin-hair conditions such as, e.g. acne, seborrhoea, female hirsutism and male pattern baldness. A mammal, e.g. a human or animal, may thus be treated by a method which comprises administering thereto a pharmaceutically effective amount of a compound of formula 20 (I) or (II) or a pharmaceutically acceptable salt thereof as defined above.

The toxicity of the compounds of the invention is quite negligible so that they can be safely used in therapy. The compounds of the invention can be

- 34 -

administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar- or film-coated tablets, liquid solutions or suspensions; rectally, in the form of suppositories; parenterally, e.g. intra-muscularly, 5 or by intravenous injection or infusion; or topically, e.g. in the form of creams.

The dosage depends on the age, weight, conditions of the patient and administration route; for example, the dosage adopted for oral administration to adult humans may 10 range from about 1 to 200 mg pro dose, from 1 to 3 times daily.

As already said, the invention includes pharmaceutical compositions comprising a compound of the invention in association with a pharmaceutically acceptable 15 excipient (which can be a carrier or diluent).

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

20 For example, the solid oral forms may contain, together with the active compound, diluents, e.g., lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; 25 binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic

- 35 -

acid, alginates or sodium starch glycolate; effervescent mixtures; dye-stuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general non-toxic and pharmacologically inactive substances used in 5 pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may 10 be, e.g. syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol; in particular a syrup to be administered to diabetic patients can contain as carriers only products 15 not metabolizable to glucose, or metabolizable in very small amount to glucose, for example sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or 20 polyvinyl alcohol.

The suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycol, e.g. propylene glycol and 25 if desired, a suitable amount of lidocaine hydrochloride.

The solutions for intravenous injections or infusions may contain as carrier, for example, sterile water or

- 36 -

preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. 5 cocoa-butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

Conventional carriers may be used for topical formulations.

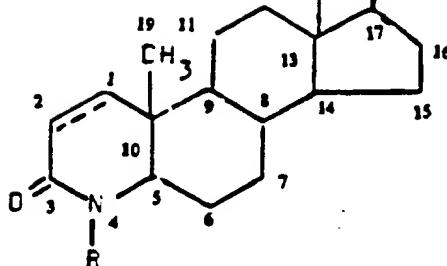
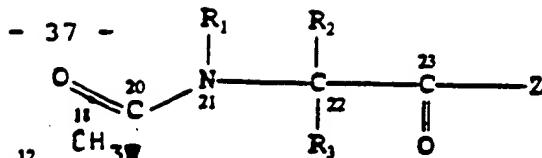
The present invention further provides a compound of 10 formula (I) or (II), or a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy in particular for use as a testosterone α -reductase inhibitor.

The present invention further provides the use of a 15 compound of formula (I) or (II) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use as a testosterone 5α -reductase inhibitor.

The following Examples further illustrate the invention.

20 The reported NMR data are determined in CDCl_3 .

The abbreviations THF, DMF, DDQ used in the present specification stand, respectively, for tetrahydrofuran, dimethylformamide and 2,3-dichloro-5,6-dicyano-benzoquinone. The nomenclature used to identify the 25 compounds in the following examples, refers to a numbering of the skeleton as shown herebelow:

EXAMPLE 1

(22R,S)-N-(1-Neopentylcarbamoyl-eth-1-yl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide.

[(I), \equiv = double bond, A = bond, R = H, R₁ = H, R₂ = CH₃,

5 R₃ = H, Z = NH-CH₂-C(CH₃)₃]

To a stirred solution of (22RS)-N-(1-neopentylcarbamoyl-eth-1-yl) 3-oxo-4-aza-5 α -androstane-17 β -carboxamide (460 mg) in anhydrous dioxane (5 ml), bis(trimethylsilyl)trifluoroacetamide (BSTFA) (1.056g) and 10 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (227 mg) were added, under nitrogen atmosphere, at room temperature.

After stirring at room temperature for 4 hours, the mixture was refluxed for 20 hours.

The resulting dark solution was poured into a stirred 15 mixture of methylene chloride (30 ml) and 1% aqueous sodium bisulphite solution (5 ml); the precipitated hydroquinone was removed by filtration, the organic layer was separated, washed with 2N HCl (5 ml), brine (5 ml) and anhydified over sodium sulphate.

20 Removal of the solvent under vacuum left a dark brown oil that was purified by flash chromatography on silica gel

- 38 -

(eluant: acetone/chloroform 1:1), so obtaining 180 mg of the title compound (m.p. 160-175°C).

NMR (DMSO) δ : 0.53 (s, 3H, Me(18)), 0.75 (s, 9H, tBu), 0.81 (s, 3H, Me(19)), 1.17 (d, 3H, -CONH-CH(CH₃)-CONH-), 2.70-3.00 (m, 2H, NH-CH₂-tBu), 3.16 (dd, 1H, H(5 α)), 4.43 (q., 1H, -CONH-CH(CH₃)-CONH-), 5.72 (bs, 1H, CONH(4)), 5.63 (dd, 1H, H(2)), 6.62 (d, 1H, H(1)), 7.35 (d, 1H, CONH(21)), 7.71 (t, 1H, CONH).

10

MS (m/z) : 457 M⁺

343 M- [CONH CH₂C(CH₃)₃]⁺ (100%)

EXAMPLE 2

(22RS)-N-(1-Neopentylcarbamoyl-1-yl) 3-oxo-4-aza-15 5 α -androstane-17 β -carboxamide.

[(I), --- = single bond, A = bond, R = H, R₁ = H, R₂ = CH₃, R₃ = H, Z = NH-CH₂C(CH₃)₃]

To a suspension of L-Alanine tert-butyl ester hydrochloride (1.136 g) in ethylacetate (25 ml), 20 triethylamine (0.87 ml) is added.

After stirring at room temperature for 30 minutes, 2-Pyridyl 3-oxo-4-aza-5 α -androstane-17 β -carbothioate (2.03g) is added and the stirring is continued for 60 hours at room temperature.

25 The mixture is poured into water (250 ml) and extracted with methylene chloride (3 x 50 ml), the combined organic extracts are washed with 1N hydrochloric acid,

- 39 -

brine, saturated sodium hydrogen carbonate, brine and anhydified over sodium sulphate.

The solvent is removed under vacuum and the crude solid (2.4 g) so obtained is chromatographed on silica gel (eluant ethyl acetate / methylene chloride 3:2), so obtaining 2.18 g of pure (22S)-N-(3-oxo-4-aza-5 α -androstane-17 β -carbonyl)alanine tert-butyl ester, which is crystallised from diethylether (1.92 g, m.p. 213-214°C).

920 mg of the tert-butyl ester so obtained are dissolved in methylene chloride (7 ml); trifluoroacetic acid (1.0 ml) is added and the solution is refluxed for 30 hours. The mixture is poured into a saturated aqueous solution of sodium bicarbonate (25 ml), and the organic layer is separated; the aqueous layer is washed twice with methylene chloride and acidified to pH 1-2 by slow addition of 1N hydrochloric acid; the precipitation of the free acid occurs; after aging overnight at room temperature, the precipitate is filtered and dried; recrystallization from hot chloroform affords 690 mg of N-(3-oxo-4-aza-5 α -androstane-17 β -carbonyl)alanine (m.p. 239-241°C). Mixture of epimers 22S:22R = 85:15).

To a suspension of (22RS)-N-(3-oxo-4-aza-5 α -androstane-17 β -carbonyl)alanine (300 mg) in anhydrous toluene (5 ml), triphenylphosphine (300 mg) and dipyridyl disulfide (326 mg) were added, and the suspension was stirred for 5 hours at room temperature.

Then neopentylamine (0.629 ml) was added and the

- 40 -

clear yellow solution was stirred at room temperature for additional 24 hours.

The solvent was removed under vacuum and the crude was chromatographed directly on silica gel eluting with 5 acetone/chloroform 3:2, to give 240 mg of the title compound (m.p. 140-150°C).

NMR (DMSO) δ : 0.53 (s, 3H, Me(18)), 0.75 (s, 3H, Me(19)), 0.80 (s, 9H, tBu), 1.17 (d, 3H, -CONH-CH(CH₃)-CONH-), 2.70-3.00 (m, 3H, 10 NH-CH₂-tBu + H(5 α)), 4.43 (q, 1H, -CONH-CH(CH₃)-CONH-), 7.25 (bs, 1H, CONH(4)), 7.35 (d, 1H, CONH(21)), 7.71 (t, 1H, CONH).

MS (m/z) : 459 M⁺⁺

15 345 M - [CONH CH₂C(CH₃)₃]¹⁺ (100%)

EXAMPLE 3

(22RS)-N-(3-oxobut-2-yl) 3-oxo-4-aza-5 α -androstane-17 β -carboxamide.

[(I), — = single bond, A = bond, R = H, R₁ = H, R₂ = CH₃, 20 R₃ = H, Z = CH₃]

To a stirred suspension of (22RS)-(3-oxo-4-aza-5 α -androstane-17 β -carbonyl)alanine 2-pyridylthioester (725.5 mg) in anhydrous tetrahydrofuran (30 ml), cooled to -78°C, under an argon atmosphere, a solution of methylmagnesium 25 bromide (6 ml, in tetrahydrofuran/toluene 25:75) is added dropwise.

The reaction mixture is stirred at -78°C for 30

- 41 -

minutes, allowed to rise to -30°C and then quenched with 10% ammonium chloride; the resulting solution is extracted with ethyl acetate and the organic extracts are washed with 1N sodium hydroxide, with brine and dried over sodium sulphate.

The solvent is removed under vacuum and the solid crude is chromatographed on silica gel (eluant acetone/chloroform (1:1), so obtaining 123 mg of the title compound.

10 NMR (CDCl_3) δ : 0.67 (s, 3H, Me(18)), 0.90 (s, 3H, Me(19)), 1.35 (d, 3H, $\text{CONH-CH}(\text{CH}_3)-\text{CO}$), 2.17 (s, 3H, COCH_3), 3.04 (dd, 1H, H(5 α)), 4.62 (q., 1H, $\text{CONHCH}(\text{CH}_3)\text{CO}$), 5.34 (bs, 1H, $\text{CONH}(4)$), 6.20 (d, 1H, CONH(21)).

15 MS (m/z): 388 M^{++} ; 345 $\text{M} - \text{COCH}_3^{1+}$; 274 $\text{M} - \text{CONHCH}(\text{CH}_3)\text{COCH}_3^{1+}$

EXAMPLE 4

(22RS)-N-(2,2,2-Trifluoro-1-methoxycarbonylethyl) 3-oxo-4-
20 aza-5 α -androst-1-ene-17 β -carboxamide.

[(I), --- = double bond, A = bond, R = H, R_1 = H, R_2 = CF_3 , R_3 = H, Z = OCH_3]

To a solution of 2-pyridyl 3-oxo-4-aza-5 α -androst-1-ene-17 β -carbothioate (410 mg) in methylene chloride (5.0
25 ml) 3,3,3-trifluoro-D,L-alanine methyl ester (300 mg) was added and the mixture was heated at reflux for 24 hours. The solvent was removed and the crude was chromatographed

- 42 -

on silica gel (eluant: benzene/ethyl acetate/methanol 84:11:5) so obtaining 100 mg of a white solid compound that is crystallised from AcOEt/Et₂O to afford 79 mg of the pure title compound (m.p. 113-120°C).

5 NMR (CDCl₃) δ: 0.67 (s, 3H, Me(18)), 0.96 (s, 3H, Me(19)), 3.32 (dd, 1H, H(5α)), 3.85 (s, 3H, COOCH₃), 5.40 (m, 2H, CONHCH(CF₃)CO + CONH(4)), 5.80 (dd, 1H, H(2)), 6.02 (d, 1H, CONH(21)), 6.77 (d, 1H, H(1)).

10 MS (m/z): 456 M⁺⁺
441 M - ${}^{\bullet}\text{CH}_3$ ¹⁺
438 M - ${}^{\bullet}\text{H}_2\text{O}$ ¹⁺⁺
425 M - ${}^{\bullet}\text{OCH}_3$ ¹⁺

Following an analogous procedure and using the
15 appropriate starting materials, the compound listed below
are prepared:

N-(3,3,3-trifluoro-2-methyl-1-methoxycarbonylprop-1-yl) 3-
oxo-4-aza-5α-androst-1-ene-17β-carboxamide;
N-(4,4,4-trifluoro-3-methyl-1-methoxycarbonylbut-1-yl) 3-
20 oxo-4-aza-5α-androst-1-ene-17β-carboxamide.

EXAMPLE 5

(22S)-N-(3-oxo-hept-2-yl) 3-oxo-4-aza-5α-androst-1-ene-17β-
carboxamide.

[(I), --- = double bond, A = bond, R = H, R₁ = H, R₂ = CH₃,
25 R₃ = H, Z = nBu]

- 43 -

To a stirred solution of N-BOC-(L)-alanine (3.784 g, 20 mmol) in freshly distilled tetrahydrofuran (60 ml), a solution of n-butyl lithium (12.5 ml; 1.6 M in n-hexane) was added, dropwise, at -10°C, under a nitrogen atmosphere.

5 The clear solution was cooled at -78°C and a further amount of n-butyl lithium (25 ml, 1.6 M in n-hexane) was added dropwise.

After stirring at -78°C for $\frac{1}{2}$ h the reaction mixture was allowed to reach room temperature and, after 1 h at 10 room temperature the reaction was poured into a diluted solution of ammonium chloride and ice (400 ml) and extracted with ether (3 x 100 ml).

15 The organic extracts were washed with saturated ammonium chloride solution, with brine, with water and anhydified over sodium sulphate.

Evaporation of the solvent under vacuum affords a crude oil that is purified by flash chromatography on silica gel (eluant ethyl acetate/n-hexane 20:80), so obtaining 1.45g of (2S)-N-BOC-2-aminoheptan-3-one.

20 (2S)-N-BOC-2-aminoheptan-3-one (1.45g) was dissolved in ethyl acetate (25 ml); the solution was cooled at about -50°C and saturated with gaseous hydrochloric acid.

After stirring at room temperature overnight, the solvent was removed under vacuum and the yellow oil so 25 obtained was treated with diethyl ether (5ml), thus affording 662 mg of (2S)-2-aminoheptan-3-one hydrochloride as a white solid. To a stirred solution of 2-pyridyl 3-

- 44 -

oxo-4-aza-5 α -androst-1-ene-17 β -carbothioate (340 mg) in anhydrous methylene chloride (20 ml) and triethylamine (0.694 ml), a solution of (S)-2-aminoheptan-3-one hydrochloride (410 mg) in anhydrous methylene chloride (25 ml) is added dropwise during 1 hour.

The mixture is stirred at room temperature for 18 hours and then the solvent is removed under vacuum and the yellow crude is chromatographed on silica gel (eluant: chloroform/ethyl acetate 50:50), so affording 210 mg of the title compound (m.p. 218-220°C from ethyl acetate).

Elemental analysis

Calculated for C₂₆H₄₀N₂O₃: C 72.86 H 9.41 N 6.53

found: C 72.42 H 9.05 N 6.46

NMR (CDCl₃) δ : 0.68 (s, 3H, Me(18)), 0.90 (t, 3H, 15 (CH₂)₃CH₃), 0.96 (s, 3H, Me(19)), 1.35 (d, 3H, -CONH-CH(CH₃)CO-), 2.50 (2dt, 2H, COCH₂CH₂-), 3.26 (dd, 1H, H(5 α)), 4.62 (q, 1H, -CONHCH(CH₃)CO-), 5.34 (bs, 1H, CONH(4)), 5.81 (dd, 1H, H(2)), 6.20 (d, 20 1H, CONH(21)), 6.77 (d, 1H, H(1)).

IR (nujol): 3410, 3190, 1712, 1665, 1600 cm⁻¹

MS (m/z): 428 M⁺

343 M - ¹CO(CH₂)₃CH₃¹⁺

272 M - ¹CONHCH(CH₃)CO(CH₂)₃CH₃¹⁺ (100%)

25 **EXAMPLE 6**

(22S)-N-(3-methylthio-1-methoxycarbonylprop-1-yl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide

- 45 -

[(I), = double bond, A = bond, R = H, R₁ = H, R₂ = CH₂CH₂SCH₃, R₃ = H, Z = OCH₃]

To L-methionine methyl ester hydrochloride (206.3 mg) in methylene chloride (5 ml), triethylamine (0.138 ml) is 5 added; after 10 minutes 2-pyridyl 3-oxo-4-aza-5 α -androst-1-ene-17 β -carbothioate (826 mg) is added to the cloudy solution.

After stirring at room temperature for 24 hours, the mixture is loaded directly on a silica gel column and 10 eluted with methylene chloride/ethyl acetate 50:50, so obtaining 300 mg of solid yellow compound, which is crystallised from boiling ethyl acetate/methylene chloride (3:1). After filtering and drying under vacuum, 230 mg of the title compound are obtained (m.p. 228-229°C).

15

Elemental analysis

Calculated for C₂₅H₃₈N₂O₄S: C 64.90 H 8.28 N 6.05 S 6.93

found: C 64.48 H 8.15 N 5.95 S 7.09

20 NMR (CDCl₃) δ : 0.68 (s, 3H, Me(18)), 0.96 (s, 3H, Me(19)), 2.00 (m, 2H, -CH-CH₂CH₂SCH₃), 2.10 (s, 3H, SCH₃), 2.55 (t, 2H, -CH₂SCH₃), 3.32 (dd, 1H, H(5 α)), 3.75 (s, 3H, COOCH₃), 4.85 (m, 1H, CONHCHCO), 5.25 (bs, 1H, CONH(4)), 5.81 (dd, 1H, H(2)), 6.03 (d, 1H, CONH(21)), 6.78 (d, 1H, H(1)).

25

MS (m/z): 462 M⁺

- 46 -



Following an analogous procedure and using the appropriate starting materials, the compounds listed below 5 are prepared:

$\text{N}-(2\text{-methoxy-1-methoxycarbonyl-1-yl})\ 3\text{-oxo-4-aza-5}\alpha\text{-androst-1-ene-17}\beta\text{-carboxamide.}$

EXAMPLE 7

$(22\text{RS})\text{-N-}(5\text{-methyl-2-oxohex-3-yl})\ 3\text{-oxo-4-aza-5}\alpha\text{-androst-1-10 ene-17}\beta\text{-carboxamide.}$

[(I), $\text{---} = \text{double bond}$, $\text{A} = \text{bond}$, $\text{R} = \text{H}$, $\text{R}_1 = \text{H}$, $\text{R}_2 = -\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{R}_3 = \text{H}$, $\text{Z} = \text{CH}_3$]

A suspension of D,L leucine (1.0 g) in pyridine (3.34 ml) and acetic anhydride (3.34 ml) is refluxed for 6.0 15 hours and then at room temperature overnight.

After diluting with water and 1N hydrochloric acid, the mixture is extracted thoroughly with methylene chloride. The organic layers are washed with 1N hydrochloric acid, with water until neutral and anhydified 20 over sodium sulphate.

After evaporating the solvent, the crude brownish oil is purified by flash chromatography on silica gel (eluant: methylene chloride/acetone 90:10), so obtaining 624 mg of (3RS)-N-acetyl-3-amino-5-methylhexan-2-one as a clear oil. 25 To (3RS)-N-acetyl-3-amino-5-methylhexan-2-one (564 mg) dissolved in acetic acid (2.2 ml), concentrated

- 47 -

hydrochloric acid (4 ml) is added and the mixture is refluxed for 6 hours. The solvents are evaporated under vacuum, the crude is treated with a little anhydrous ethanol and the product is precipitated by slow addition of 5 diethylether.

After filtering, washing with diethyl ether and drying under vacuum, 383 mg of (3R,S)-3-amino-5-methylhexan-2-one hydrochloride are obtained.

A mixture of 2-pyridyl 3-oxo-4-aza-5 α -androst-1-ene-10 17 β -carbothioate (450 mg) in methylene chloride (22 ml) and (3R,S)-3-amino-5-methylhexan-2-one hydrochloride (271 mg) is treated with triethylamine (0.458 ml).

The yellow solution is stirred at room temperature for 5 days.

15 After removing the solvent under vacuum the crude is purified by flash chromatography (eluant: methylene chloride/acetone 75:25), so obtaining 530 mg of the title compound.

20 Elemental analysis

Calculated for C₂₆H₄₀N₂O₃ : C 72.86 H 9.41 N 6.53
found : C 71.40 H 9.50 N 6.28

NMR (CDCl₃) δ : 0.65 (s, 3H, Me (18)), 0.94 (s + d, 9H, Me (19) + CH(CH₃)₂), 2.11 (s, 3H, COCH₃), 3.31 (dd, 1H, H(5 α)), 4.70 (m, 1H, CONH-CH-COCH₃), 5.48 (s, 1H, CONH(4)), 5.80 (dd, 1H, H(2)), 5.87 (d, 1H, CONH(21)),

- 48 -

6.77 (d, 1H, H(1)).

MS (m/z): 428 M⁺

413 M - $\cdot\text{CH}_3\text{]}^+$

385 M - $\cdot\text{CH}(\text{CH}_3)\text{]}^+$

5 300 385 - $\cdot\text{C}_4\text{H}_7\text{NO}\text{]}^+$

272 300 - CO]^+

86 $\cdot\text{C}_5\text{H}_{12}\text{N}\text{]}^+$ (100%)

Following an analogous procedure and using the appropriate starting materials, the compounds listed below 10 are prepared:

(22RS)-N-(3-oxobut-2-yl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide.

NMR (CDCl₃) δ : 0.65 and 0.68 (2s, 3H, Me(18)), 0.97 (s, 3H, Me(19)), 1.38 (d, 3H, -NHCH(CH₃)COCH₃), 2.24 15 (s, 3H, COCH₃), 3.33 (dd, 1H, H(5 α)), 4.63 (m, 1H, NHCH(CH₃)COCH₃), 5.40 (s, 1H, NH(4)), 5.80 (dd, 1H, H(2)), 6.10 and 6.20 (2d, 1H, NH(21)), 6.78 (d, 1H, H(1)).

MS (m/z): 386 M⁺

20 371 M - $\cdot\text{CH}_3\text{]}^+$

343 M - $\cdot\text{COCH}_3\text{]}^+$

(22RS)-N-(4-methyl-2-oxopent-3-yl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide

NMR (CDCl₃) δ : 0.75 and 0.81 (2s, 3H, Me(18)), 0.96 (s, 3H, Me(19)), 0.79 and 1.02 (2d, 6H, isopropylidene methyls), 2.03 (s, 3H, COCH₃), 3.33 (dd, 1H, H(5 α)), 4.72 (m, 1H, H(22)), 5.25 (s, 1H,

- 49 -

NH(4)), 5.81 (dd, 1H, H(2)), 5.85 and 5.92 (2d, 1H, NH(21)), 6.78 (d, 1H, H(1)).

MS (m/z): 414 M⁺

N-(4-methyl-2-oxohex-3-yl) 3-oxo-4-aza-5 α -androst-1-ene-

5 17 β -carboxamide;

N-(5,5,5-trifluoro-4-methyl-2-oxopent-3-yl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-(6,6,6-trifluoro-5-methyl-2-oxohex-3-yl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

10 N-(5-methylthio-2-oxopent-3-yl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-(4-methoxy-2-oxobut-3-yl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide.

EXAMPLE 8

15 (22RS)-N-(1,1,1-trifluoro-3-oxobut-2-yl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide.

[(I): --- = double bond, A = single bond, R = H, R₁ = H, R₂ = CF₃, R₃ = H, Z = CH₃]

D,L-Trifluoroalanine (159 mg) in dry pyridine (0.6 ml) is treated with acetic anhydride (0.6 ml) and stirred at room temperature for 4.5 hours. The reaction mixture is then acidified with 1N hydrochloric acid and extracted several times with methylene chloride; the combined organic layers are washed with water, dried over sodium sulphate and evaporated. The crude so obtained is purified by flash chromatography (eluant: methylene chloride/ethyl acetate

- 50 -

80:20) to afford 117 mg of (2RS)-N-acetyl 1,1,1-trifluoro-2-aminobutan-3-one.

A solution of the α -acetylaminoketone (50 mg) in 1 ml of a mixture of concentrated hydrochloric acid/5 ethanol/water (2:1:1) is refluxed for 6 hours. The reaction mixture is evaporated to dryness under vacuum, the residue is dissolved in the minimum amount of absolute ethanol and diethyl ether is added dropwise until further addition causes no more precipitation. The precipitate is 10 collected by filtration, washed with ether and dried, so obtaining 20 mg of (2RS)-1,1,1-trifluoro-2-aminobutan-3-one hydrochloride. A stirred solution of 2-pyridyl 3-oxo-4-aza-5 α -androst-1-ene-17 β -carbothioate (237 mg) and (2RS)-1,1,1-trifluoro-2-amino-butan-3-one hydrochloride (153 mg) 15 in methylene chloride (10 ml) is treated dropwise with triethylamine (0.241 ml). After 4 hours the reaction mixture is evaporated to dryness and the crude is purified by flash chromatography (eluant: methylene chloride/acetone 60:40), so affording 93 mg of the title compound.

20 NMR ($CDCl_3$) δ : 0.67 (s, 3H, Me(18)), 0.96 (s, 3H, Me(19)), 2.11 (s, 3H, $-COCH_3$), 3.32 (dd, 1H, H(5 α)), 5.25 (m, 1H, CONH-CH(CF₃)-CO-), 5.40 (s, 1H, CONH(4)), 5.80 (dd, 1H, H(2)), 6.02 (d, 1H, CONH(21)), 6.77 (d, 1H, H(1)).

25 EXAMPLE 9

(22RS)-N-(1,1,1-trifluoro-2-oxobut-3-yl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide.

- 51 -

[(I): --- = double bond, A = single bond, R = H, R₁ = H, R₂ = CH₃, R₃ = H, Z = CF₃]

D,L-Alanine is N-benzoylated by standard procedures and the benzamido derivative (1.59g) is cyclized to the 5 corresponding oxazol-5-one by brief (- 15 minutes) warming to 80°C with acetic anhydride (2.9 ml). The reaction mixture is then concentrated under vacuum in a rotatory evaporator and vacuum distilled twice with toluene.

The residue is treated with trifluoroacetic anhydride 10 (3.1 ml) and heated under reflux for 1.75 hours and then at room temperature overnight. The volatiles are then removed thoroughly under vacuum and the residue is treated with oxalic acid (1.2 g) and stirred at 110°C for 20 minutes. The reaction mixture is then diluted with water, and 15 extracted with ethyl acetate (5 x 30 ml); the organic layers are anhydified over sodium sulphate and the solvent evaporated under vacuum.

The crude so obtained is purified by flash chromatography on silica gel (eluant: ethyl acetate/n- 20 hexane 30:70) to afford a solid material that is crystallized from carbon tetrachloride; there are obtained 410 mg of (3RS)-N-benzoyl 1,1,1-trifluoro-3-aminobutan-2-one, partially in the hydrate form.

A solution of the ketone-hydrate mixture (404 mg) in 25 ethanol (3 ml), cooled to 0°C, is treated with sodiumborohydride (NaBH₄, 62 mg). The reaction mixture is stirred at room temperature for 4 hours, then it is

- 52 -

acidified with 6N hydrochloric acid and extracted with ethyl acetate; the organic extracts are washed with water, dried over sodium sulphate and flush-evaporated to afford 404 mg of (2RS-3RS)-N-benzoyl 1,1,1-trifluoro-3-aminobutan-5-ol.

A solution of trifluorobenzamidoalcohol (333 mg) in 94 ml of a mixture of concentrated hydrochloric acid/ethanol/water (2:1:1) was stirred under reflux for 23 hours. The reaction mixture was then evaporated under 10 vacuum and the residue dissolved in water (13 ml) and extracted several times with diethyl ether. Flush evaporation of the aqueous layer afforded a pale-green solid that, after trituration with ethyl acetate, gave 190 mg of (2RS-3RS)-1,1,1-trifluoro-3-amino-butan-2-ol hydrochloride as a white solid (mixture of both pairs of enantiomers).

A stirred solution of 2-pyridyl 3-oxo-4-aza-5 α -androstan-1-ene-17 β -carbothioate (344 mg) and (2RS-3RS)-1,1,1-trifluoro-3-amino-butan-2-ol hydrochloride in 20 methylene chloride (14 ml) is treated dropwise with triethylamine (0.175 ml). After 2 days the reaction mixture was evaporated to dryness and purified by flash chromatography on silica gel (eluant: methylene chloride/acetone 70:30) to afford 338 mg of (22RS-23RS)-N-(1,1,1-trifluoro-2-hydroxybut-3-yl) 3-oxo-4-aza-5 α -androstan-1-ene-17 β -carboxamide [(II), --- = double bond, A = single bond, R = H, R₁ = H, R₂ = CH₃, R₃ = H, Z = CF₃].

- 53 -

MS (m/z) : 442 M⁺ (100%)

427 M - 'CH₃]⁺

5



IR (CHCl₃) : 1700, 1670 cm⁻¹

NMR (CDCl₃) δ: 0.70 (s, 3H, Me(18)), 0.97 (s, 3H, Me(19)),
 1.3 (d, 3H, CONHCH₂CH(OH)-), 3.33 (dd, 1H,
 10 H(5α)), 4.05 (m, 1H, -CH(OH)CF₃), 4.31 (m,
 1H, CONHCH₂(CH₃)), 4.90 and 5.05 (2m, 1H,
 OH), 5.39 (s, 1H, NH(4)), 5.54 (m, 1H,
 NH(21)), 5.8 (dd, 1H, H(2)), 6.78 (d, 1H,
 H(1)).

15

A solution of (22RS-23RS)-N-(1,1,1-trifluoro-2-hydroxybut-3-yl) 3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (110 mg) in methylene chloride (1.1 ml) is added within 20 minutes to a stirred solution of oxalyl chloride (0.095 ml) and dimethylsulfoxide (0.171 ml) in 20 methylene chloride (2.0 ml), prepared according to the usual procedure, at -10°C. The reaction temperature is maintained for 15 minutes, triethylamine (0.173 ml) is added dropwise and then the mixture is allowed to warm to room temperature. Water is added and the aqueous layer is 25 extracted several times with ethyl acetate.

The combined organic extracts are washed with water, dried over sodium sulphate and the solvent is removed under vacuum.

- 54 -

Purification of the crude by flash chromatography (methylene chloride/acetone 70:30) affords 73 mg of the title compound, as a mixture of trifluoroketone and its hydrate form.

5 MS (m/z): 458 M⁺⁺ hydrated form

440 M⁺⁺ ketone form

425 M - ${}^{\bullet}\text{CH}_3\text{]}^+$

343 M - ${}^{\bullet}\text{COCF}_3\text{]}^+$

300 M - ${}^{\bullet}\text{NH-CH}(\text{CH}_3)\text{COCF}_3\text{]}^+$

10 IR (CDCl₃): 3260, 3170, 1770, 1700, 1670 cm⁻¹

NMR (CDCl₃) δ: 0.70 (s, 3H, Me(18)), 0.97 (s, 3H, Me(19)),
1.35 and 1.45 (2d, 3H, NHCH(CH₃)COCF₃, hydrate
and ketone forms), 3.33 (dd, 1H, H(5α)),
4.15 and 5.00 (2m, 1H, NHCH(CH₃)COCF₃, hydrate
and ketone forms), 5.70 - 6.05 (m, NH(4) +
NH(21) hydrate and ketone forms + OH hydrate
form), 5.80 (dd, 1H, H(2)), 6.78 (d, 1H,
H(1)).

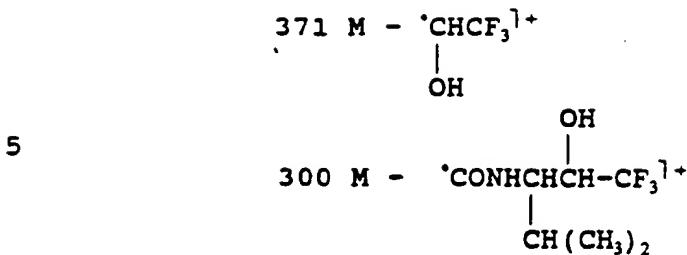
Following an analogous procedure and using the D,L-

20 valine as starting material, (22RS-23RS)-N-(1,1,1-trifluoro-4-methyl-2-hydroxypent-3-yl) 3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide [(II): --- = double bond,
A = single bond, R = H, R₁ = H, R₂ = CH(CH₃)₂, R₃ = H,
Z = CF₃] is prepared:

25 MS (m/z): 470 M⁺⁺

455 M - ${}^{\bullet}\text{CH}_3\text{]}^+$

- 55 -



5

NMR (CDCl₃) δ: 0.78 (s, 3H, Me(18)), 1.00 (s, 3H, Me(19)),
 1.00 - 1.15 (2d, 6H, CH(CH₃)₂), 3.33 (dd, 1H,
 H(5α)), 3.85 - 4.40 (2m, 2H,
 NHCH(iPr)CH(OH)CF₃), 5.10 (bm, 1H, OH), 5.45
 (d, 1H, NH(21)), 5.55 (bs, 1H, NH(4)), 5.80
 (dd, 1H, H(2)), 6.80 (d, 1H, H(1)).

15

15 The oxidation of this compound by the Swern reagent
affords (22RS)-N-(1,1,1-trifluoro-4-methyl-2-oxo-pent-3-yl)
3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide [(I): =
double bond, A = single bond, R = H, R₁ = H, R₂ = CH(CH₃)₂, -
R₃ = H, Z = CF₃] as a mixture or epimers almost exclusively
20 in the ketone form.

20 in the ketone form.

MS (m/z): 486 M⁺ hydrated form

468 M^{++} ketone form

453 M - $\cdot\text{CH}_3\text{]}^+$

371 M = COCl_2^+

25

300 M - NHCH-COCl₂¹⁺

$$\text{CH}(\text{CH}_3)_2$$

NMR (CDCl₃) δ: 0.64 and 0.70 (2s, 1H, Me(18)), 0.97 (s, 3H, Me(19)), 0.85 and 1.05 (4d, 6H, CH(CH₃)₂), 3.33 (dd, 1H, H(5α)), 5.05 (2m, 1H, NH-

- 56 -

CH(iPr)COCF₃), 5.55 (s, 1H, NH(4)), 5.63 and
5.75 (2d, 1H, NH(21)), 5.80 (dd, 1H, H(2)),
6.77 (d, 1H, H(1)).

Following an analogous procedure and using
5 phenylalanine as starting material, N-(1,1,1-trifluoro-2-
oxo-4-phenylbut-3-yl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -
carboxamide was obtained.

Following an analogous procedure and using
pentafluoropropionic anhydride instead of trifluoroacetic
10 anhydride, the corresponding pentafluoroketones are
obtained, e.g., starting from alanine, N-(1,1,1,2,2-
pentafluoro-3-oxopent-4-yl) 3-oxo-4-aza-5 α -androst-1-ene-
17 β -carboxamide was obtained.

15 EXAMPLE 10

N-(1,1,1-trifluoro-3-methyl-2-oxobut-3-yl) 3-oxo-4-aza-5 α -
androst-1-ene-17 β -carboxamide.

[(I): --- = double bond, A = single bond, R = H, R₁ = H, R₂
= CH₃, R₃ = CH₃, Z = CF₃]

20 A mixture of trifluoroacetaldehyde ethyl hemiacetal
(2.58 ml), 2-nitropropane (1.81 ml) and potassium carbonate
(111 mg) is stirred at 65°C (oil bath temperature) for 6
hours followed by 2.5 days at room temperature. The
reaction mixture is diluted with water (100 ml) and
25 extracted with methylene chloride (100 ml + 5 x 50 ml).
The combined organic layers are dried over sodium sulphate
and the solvent is evaporated under reduced pressure.

- 57 -

Purification of the liquid residue by flash chromatography on silica gel (eluant n-hexane/ethylacetate 85:15) affords 3-methyl-3-nitro-1,1,1-trifluorobutan-2-ol as an oil (2.005 g)

5 NMR (CDCl₃) δ: 1.75 (m, 6H, 2CH₃), 3.1 (m, 1H, OH), 4.75 (m, 1H, CF₃CH-)

The β-nitroalcohol (2.005g) in 95% ethanol (50ml) is reduced in a Parr shaker under 50 psi of hydrogen pressure, with Raney Nickel (W-2) as catalyst. The catalyst is 10 filtered off, the solution is treated with 37% hydrochloric acid and the solvent is evaporated under vacuum, so affording a solid residue which is further purified by recrystallisation from ethanol/diethyl ether : 1,663 g of (2RS)-3-amino-3-methyl-1,1,1-trifluoro-butan-2-ol 15 hydrochloride are obtained (m.p. 237-245° dec).

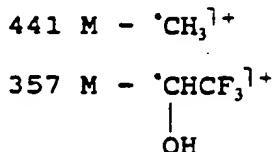
A stirred solution of 2-pyridyl 3-oxo-4-aza-5α-androst-1-ene-17β-carbothioate (500 mg) and (2R,S)-3-amino-3-methyl-1,1,1-trifluoro-butan-2-ol hydrochloride (470 mg) in anhydrous dimethylformamide (20 ml) is treated dropwise 20 with triethylamine (0.509 ml) and then is heated to 100°C for 18 hours.

After diluting with benzene to a volume of about 150 ml, the reaction mixture is washed with water (150 ml) with 1N hydrochloric acid (2 x 25 ml), with water until neutral 25 and dried over sodium sulphate. The solvent is evaporated under vacuum and the crude residue is purified by flash chromatography on silica gel (eluant: Benzene/ethyl-

- 58 -

acetate/methanol 82:10:8) to yield 466 mg of (23RS)-N-(1,1,1-trifluoro-2-hydroxy-3-methylbut-3-yl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide [(II): — = double bond, A = single bond, R = H, R₁ = H, R₂ = CH₃, R₃ = CH₃, Z = CF₃]

5 MS (m/z) : 456 M⁺



10

¹H NMR (CDCl₃) δ: 0.70 (s, 3H, Me(18)), 0.97 (s, 3H, Me(19)), 1.40 and 1.50 (2s, 6H, NH-C(CH₃)₂-CH(OH)CF₃), 3.33 (m, 1H, H(5α)), 3.70 (m, 1H, OH), 3.90 (m, 1H, -CH(OH)CF₃), 5.45 (s, 1H, NH(4)), 5.70 (s, 1H, NH(21)), 5.82 (dd, 1H, H(2)), 6.77 (d, 1H, H(1)).

A solution of (23RS)-N-(1,1,1-trifluoro-2-hydroxy-3-methylbut-3-yl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (250 mg) in methylene chloride (3 ml) is added, 20 within 20 minutes, to a stirred solution of oxalyl chloride (0.211 ml) and dimethylsulfoxide (0.373 ml) in methylene chloride (7 ml) (prepared according to the Swern procedure at about -60°C), maintaining the temperature at -21°C, under an inert atmosphere of nitrogen. After 15 minutes 25 triethylamine (0.381 ml) is added dropwise and then the reaction mixture is allowed to warm to room temperature.

After staying at room temperature overnight the mixture is diluted with methylene chloride (70 ml) and water (30 ml); the organic layer is separated, is dried

- 59 -

over sodium sulphate and the solvent is evaporated under reduced pressure.

The crude foam so obtained is purified by flash chromatography on silica gel (eluant : methylene chloride/acetone 80:20) to yield the title compound, as a foam which solidifies by treatment with diethylether (m.p. 283-286°C), almost completely in the ketone form.

MS (m/z) : 472 M⁺⁺ hydrate form

454 M⁺⁺ ketone form

10 439 M - 'CH₃]¹⁺

357 M - 'COCF₃]¹⁺

300 M - 'NH-C(CH₃)₂COCF₃]¹⁺

NMR (CDCl₃) δ: 0.68 (s, 3H, Me(18)), 0.97 (s, 3H, Me(19)),
1.52 (s, 6H, NH-C(CH₃)₂-COCF₃), 3.33 (dd, 1H,
15 H(5α)), 5.45 (s, 1H, NH(4)), 5.75 (s, 1H,
NH(21)), 5.82 (dd, 1H, H(2)), 6.77 (d, 1H,
H(1)).

Following an analogous procedure and using the appropriate starting material the below reported compounds 20 were obtained:

N-(3-methyl-2-oxobut-3-yl) 3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide [(I): --- = double bond, A = single bond, R = H, R₁ = H, R₂ = CH₃, R₃ = CH₃, Z = CH₃];
N-(1,1,1-trifluoro-2-oxo-3-phenylpropyl) 3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;
25 N-(1,1,1-trifluoro-3-methyl-2-oxo-3-phenylpropyl) 3-oxo-4-

- 60 -

aza-5 α -androst-1-ene-17 β -carboxamide.

EXAMPLE 11

(22RS)-N-(4,4-dimethyl-2-oxopent-3-yl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide [(I): --- = double bond, A = 5 single bond, bond, R = H, R₁ = H, R₂ = CH(CH₃)₃, R₃ = H, Z = CH₃]

To a stirred solution of (L)-tert-butyl-leucine (3.1 g) in 1N sodium hydroxide (23.6 ml), maintained at about 15°C, ethyl chloroformate (2.3 ml) is added portionwise 10 over about 1 hour while maintaining the pH between 9.0 and 9.5 by eventual addition of 1N sodium hydroxide.

After stirring for half an hour at pH 9.5, the solution is cooled to 0°C, washed twice with diethylether, acidified with 40% phosphoric acid to pH 1.0 and extracted 15 with methylene chloride. The organic extracts are dried over sodium sulphate and the solvent is removed under vacuum.

The crude is purified by chromatography on silica gel (eluant n-hexane/ethylacetate/acetic acid 70:30:1) so 20 affording 4.5 g of N-(ethoxycarbonyl)-L-tert-butyl-leucine.

To N-(ethoxycarbonyl)-L-tert-butyl-leucine (980 mg) dissolved in freshly distilled tetrahydrofuran (25 ml) methyl lithium (2.78 ml of a 1.57 M solution in diethyl ether) is added while cooling at -10°C under inert 25 atmosphere of nitrogen.

After stirring at -10°C for 15 minutes, the reaction mixture is cooled to about -40°C and further methyl lithium

- 61 -

(8.37 ml of a 1.57 M solution in diethylether) is added.

After stirring at -35°C for 1 hour the reaction mixture is allowed to warm to room temperature and stirred for 14 hours, and then it is poured into ice-cooled 40% 5 H_3PO_4 (100 ml) and extracted with ethyl acetate (4 x 50 ml). The organic extracts are washed with $NaHCO_3$, with brine, dried over sodium sulphate and the solvent is evaporated under vacuum. The crude is purified by chromatography on silica gel (eluant n-hexane/ethylacetate 10 80:20) thus affording 140 mg of N-ethoxycarbonyl-3-amino-4,4-dimethyl-pentan-2-one.

N-ethoxycarbonyl-3-amino-4,4-dimethyl-pentan-2-one (203 mg) is dissolved in 48% aqueous hydrobromic acid (4 ml) and the solution is stirred under reflux for 6 hours. 15 The reaction mixture is then evaporated under reduced pressure to give a solid residue, that is further purified by recrystallisation (from ethanol/diethylether) to afford 149 mg of pure (3RS)-3-amino-4,4-dimethyl-pentan-2-one hydrobromide (m.p. 218-220°C)

20 NMR ($CDCl_3$) δ : 1.1 (s, 9H, tBu), 2.35 (s, 3H, $COCH_3$), 4.15 (s, 1H, $-CH(tBu)$)

A solution of 2-pyridyl 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxylate (100 mg) and (3RS)-3-amino-4,4-dimethyl-pentan-2-one hydrobromide (64 mg) in methylene chloride (4 25 ml) is treated dropwise with triethylamine (0.051 ml) and the mixture is stirred at room temperature for 3.5 days. The solvent is evaporated under reduced pressure and the

- 62 -

residue is purified by flash chromatography on silica gel (eluant methylene chloride/acetone 80:20) to yield 81 mg of the title compound (1:1 mixture of both epimers)

MS (m/z): 428 M⁺

5 NMR (CDCl₃) δ: 0.62 and 0.72 (2s, 3H, Me(18)), 0.97 (s, 3H, Me(19)), 1.00 (s, 9H, tBu), 2.28 (s, 3H, COCH₃), 3.33 (dd, 1H, H(5α)), 4.55 (m, 1H, CH(tBu)), 5.38 (s, 1H, NH(4)), 5.81 (dd, 1H, H(2)), 5.90 (m, 1H, NH(21)), 6.78 (d, 1H, H(1)).

10

EXAMPLE 12

(22RS)-N-(1,1,1-trifluoro-2-oxobut-3-yl) 3-oxo-4-aza-5α-androstan-17β-carboxamide [(I): --- = double bond, A = single bond, R = H, R₁ = H, R₂ = CH₃, R₃ = H, Z = CF₃]

15 To a stirred solution of (2RS-3RS)-1,1,1-trifluoro-3-amino-butan-2-ol hydrochloride (525 mg) (obtained as described in the example 9) in methylene chloride (30 ml), triethylamine (0.39 ml) is added, at room temperature. After 30 minutes solid 2-pyridyl 3-oxo-androst-4-ene-17β-20 carbothioate (1.00 g) is added and the mixture is refluxed for 24 hours. After diluting with methylene chloride the reaction mixture is washed with 1N hydrochloric acid, water until neutrality and dried over sodium sulphate. The solvent is removed under vacuum and the crude (1.1 g) is 25 purified by flash chromatography (eluant: n-hexane/ethylacetate 60:40) so obtaining 890 mg of solid (22RS-

- 63 -

23RS)-N-(1,1,1-trifluoro-2-hydroxybut-3-yl) 3-oxo-androst-4-ene-17 β -carboxamide [(XII): A = single bond, R₁ = H, R₂ = CH₃, R₃ = H, Z = CF₃]

To a solution of (22RS-23RS)-N-(1,1,1-trifluoro-2-hydroxybut-3-yl) 3-oxo-androst-4-ene-17 β -carboxamide (690 mg) in tert-butanol (9 ml) and 2M aqueous sodium carbonate (1.04 ml), a 2% aqueous potassium permanganate solution (0.882 ml) and a 0.75 M sodium metaperiodate aqueous solution (17.5 ml) are added dropwise simultaneously, at such a rate that the colour of the reaction mixture remains always pink (over about 30 minutes) at about 35-40°C.

After stirring at 40°C for 3 hours, the reaction mixture is cooled to 30°C, filtered and the tert-butanol is removed under vacuum. By slow addition of 1N hydrochloric acid, at about 0°C, the precipitation of the crude keto-acid occurs. Purification of the crude by flash chromatography (eluant ethyl acetate/n-hexane 70/30) affords 260 mg of (22RS-23RS)-17 β -[N-(1,1,1-trifluoro-2-hydroxybut-3-yl)carbamoyl]-5-oxo-4-nor-3,5-secoandrostan-3-oic acid [(IX): A = single bond, R₁ = H, R₂ = CH₃, R₃ = H, Z = CF₃]

A suspension of the secoacid so obtained (260 mg) in ethylene glycol (3.0 ml) is saturated at 0°C with gaseous ammonia: the secoacid dissolves completely. The solution so obtained is heated slowly at 180°C over about 1 hour and maintained at this temperature for 20 minutes.

After cooling to room temperature and diluting with

- 64 -

water, the reaction mixture is extracted with methylene chloride. The combined organic extracts are washed with water until neutrality, dried over sodium sulphate and the solvent is evaporated under vacuum.

5 Purification of the brown crude so obtained, by flash chromatography on silica gel (eluant: methylene chloride/acetone 80:20) affords 150 mg of (22RS-23RS)-N-(1,1,1-trifluoro-2-hydroxybut-3-yl) 3-oxo-4-aza-androst-5-ene-17 β -carboxamide. [(XI): A = single bond, R = H, R₁ = 10 H, R₂ = CH₃, R₃ = H, Z = CF₃].

A solution of (22RS-23RS)-N-(1,1,1-trifluoro-2-hydroxybut-3-yl) 3-oxo-4-aza-androst-5-ene-17 β -carboxamide (150 mg) in glacial acetic acid is hydrogenated in the presence of PtO₂ (Adams' catalyst) under a pressure of 45 15 psi of hydrogen at 45°C.

The reaction mixture is cooled, the catalyst is filtered off and the solvent is removed under reduced pressure. The residue is taken up with methylene chloride, washed with 1N sulphuric acid, with brine, with sodium 20 carbonate, with brine, with water, dried over sodium sulphate and the solvent is removed under vacuum. The crude is purified by flash chromatography on silica gel (eluant methylene chloride/acetone 70:30) to afford 132 mg of (22RS-23RS)-N-(1,1,1-trifluoro-2-hydroxybut-3-yl) 3-oxo-25 4-aza-5 α -androstane-17 β -carboxamide. [(II): --- = single bond, A = single bond, R = H, R₁ = H, R₂ = CH₃, R₃ = H, Z = CF₃].

- 65 -

The oxidation of the trifluoroalcohol so obtained with the Swern reaction, analogously to the example 9, affords (22RS-23RS)-N-(1,1,1-trifluoro-2-oxo-but-3-yl) 3-oxo-4-aza-5 α -androstane-17 β -carboxamide. [(I): --- = single bond, A = single bond, R = H, R₁ = H, R₂ = CH₃, R₃ = H, Z = CH₃].

EXAMPLE 13

Scored tablets for oral use, each containing 250 mg of the active substance, were manufactured as follows.

10 Composition (for 10,000 tablets)

N-[1,1,1-trifluoro-2-oxobut-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide	2500 g
corn starch	275 g
talc powder	187 g
15 calcium stearate	38 g

The active substance was granulated with a 4% w/v aqueous solution of methyl cellulose. To the dried granules a mixture of the remainder of the ingredients is added and the final mixture compressed into tablets of 20 proper weight.

EXAMPLE 14

Two-piece hard gelatin capsules for oral use, each containing 250 mg of active substance were manufactured as follows.

25 Compositions for 10,000 capsules

- 66 -

N-[1,1,1-trifluoro-2-oxobut-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide		
lactose		2500 g
corn starch		1000 g
5 talc powder		300 g
calcium stearate		65 g
		35 g

The active substance was mixed with the starch-lactose mixture followed by the talc and calcium stearate.

EXAMPLE 15

10 Scored tablets for oral use, each containing 250 mg of the active substance, were manufactured as follows.
Composition (for 10,000 tablets)

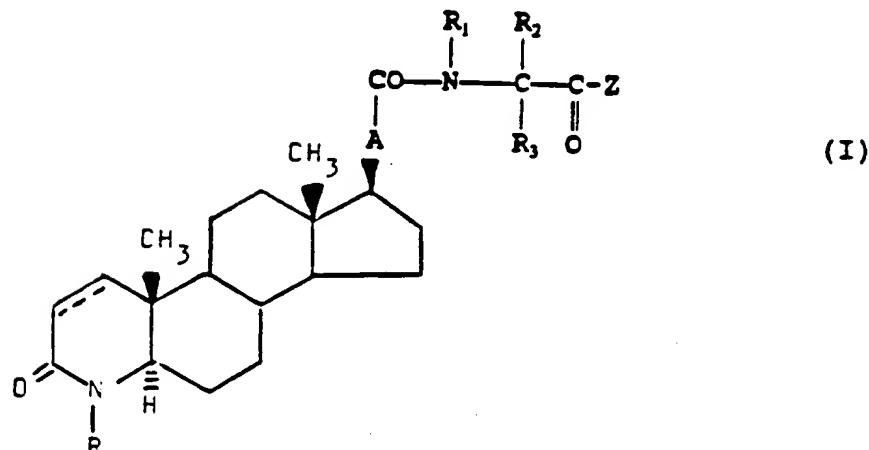
N-[1,1,1-trifluoro-2-oxobut-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide		
15 corn starch		2500 g
talc powder		280 g
calcium stearate		180 g

15 The active substance was granulated with a 4% w/v aqueous solution of methyl cellulose. To the dried granules a mixture of the remainder of the ingredients is added and the final mixture compressed into tablets of proper weight.

- 67 -

CLAIMS

1. A compound of the following formula (I):



wherein:

5 R is a hydrogen atom or a C₁-C₄ alkyl group unsubstituted or substituted by one or more fluorine atoms;

A is a single bond or a straight or branched C₁-C₆ alkylene chain;

10 R₁ is a hydrogen atom or a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms;

R₂ is:

(a) a C₁-C₆ alkyl group unsubstituted or substituted by one or more substituents chosen from fluoro, C₁-C₄ alkoxy carbonyl, carbamoyl, carboxy, hydroxy, C₁-C₄ alkoxy, amino, di-C₁-C₄ alkylamino, mercapto and C₁-C₄ alkylthio, or

20 (b) a C₅-C₇ cycloalkyl or a C₆-C₁₀ cycloalkylalkyl group, unsubstituted or substituted by one or more fluorine atoms, or

- 68 -

(c) an aryl or a C₁-C₁₀ arylalkyl group, unsubstituted or ring substituted by one or more substituents chosen from halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy and trifluoromethyl, or

5 (d) a C₆-C₁₀ heterocycloalkyl group in which the heterocyclic ring contains one or more heteroatoms chosen from N, O and S, unsubstituted or ring substituted by one or

10 more fluorine atoms;

R₃ is hydrogen, a C₁-C₄ alkyl group, or an aryl or a C₁-C₁₀ arylalkyl group, unsubstituted or ring substituted by one or more substituents chosen from halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy and trifluoromethyl;

15 Z is:

(a') a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms,

(b') an -OR₅ group wherein R₅ is a C₁-C₆ alkyl group,

20 (c') a $\begin{array}{c} R_6 \\ | \\ -N \\ \backslash \\ R_7 \end{array}$ group wherein each of R₆ and R₇, indepen-

dently, is hydrogen, C₁-C₆ alkyl, C₅-C₇ cycloalkyl or phenyl or R₆ and R₇ taken together with the nitrogen to which they are linked form a pentatomic or hexatomic saturated

25 heteromonocyclic ring, optionally containing at least one additional heteroatom selected from

- 69 -

oxygen and nitrogen; and

the symbol represents a single or a double bond; provided that when Z is a group OR₃, R₂ is not an unsubstituted C₁-C₆ alkyl group;

5 and the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein:

R is hydrogen or methyl;

A is a single bond;

R₁ is hydrogen;

10 R₂ is methyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl, trifluoromethyl, 1-trifluoromethylmeth-1-yl, 2-trifluoromethylprop-1-yl, 2-methylthioeth-1-yl, methoxymethyl, phenyl or benzyl;

R₃ is hydrogen or methyl;

15 Z is methyl, n-butyl, trifluoromethyl, pentafluoroethyl, a group OR₃ wherein R₃ is methyl, ethyl or tert-butyl,

or a group -N₃^{R₆}₁^{R₇} wherein each of R₆ and R₇,

is, independently, hydrogen, ethyl, isopropyl or neopentyl; and

20 the symbol represents a single or a double bond provided that when Z is a group OR₃, R₂ is trifluoromethyl, 1-trifluoromethylmeth-1-yl, 2-trifluoromethylprop-1-yl, 2-methylthioethyl, methoxymethyl, phenyl or benzyl.

3. A compound selected from the group consisting

- 70 -

of N-(1-neopentylcarbamoyl-eth-1-yl) 3-oxo-4-aza-5 α -androstane-17 β -carboxamide;

N-(1-neopentylcarbamoyl-eth-1-yl) 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

5 N-[3-oxobut-2-yl] 3-oxo-4-aza-5 α -androstane-17 β -carboxamide;

N-[3-oxohept-2-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-[1,1,1-trifluoro-2-oxobut-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

10 N-[4-methyl-2-oxopent-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-[1,1,1-trifluoro-4-methyl-2-oxopent-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

15 N-[5-methyl-2-oxohex-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-[4-methyl-2-oxohex-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-[4,4-dimethyl-2-oxopent-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

20 N-[1,1,1-trifluoro-3-oxobut-2-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-[2,2,2-trifluoro-1-methoxycarbonyl-eth-1-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

25 N-[5,5,5-trifluoro-4-methyl-2-oxopent-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-[3,3,3-trifluoro-2-methyl-1-methoxycarbonylprop-1-yl] 3-

- 71 -

oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-[6,6,6-trifluoro-5-methyl-2-oxohex-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-[4,4,4-trifluoro-3-methyl-1-methoxycarbonylbut-1-yl] 3-

5 oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-[5-methylthio-2-oxopent-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-[3-methylthio-1-methoxycarbonylprop-1-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

10 N-[4-methoxy-2-oxobut-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-[2-methoxy-1-methoxycarbonylth-1-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-[3-oxobut-2-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -

15 carboxamide;

N-[1,1,1-trifluoro-3-methyl-2-oxobut-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-[3-methyl-2-oxobut-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

20 N-[1,1,1-trifluoro-2-oxo-4-phenylbut-3-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-[1,1,1-trifluoro-2-oxo-3-phenylpropyl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

N-[1,1,1-trifluoro-3-methyl-2-oxo-3-phenylpropyl] 3-oxo-4-

25 aza-5 α -androst-1-ene-17 β -carboxamide; and

N-[1,1,1,2,2-pentafluoro-3-oxopent-4-yl] 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide;

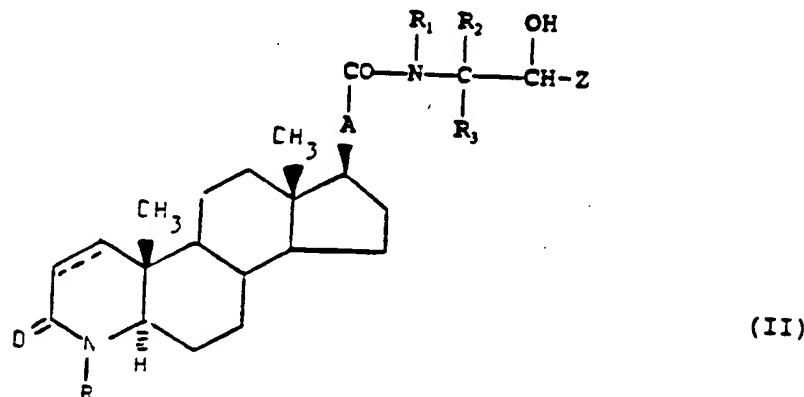
- 72 -

and the pharmaceutically acceptable salts thereof.

4. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined to claim 1 comprising:

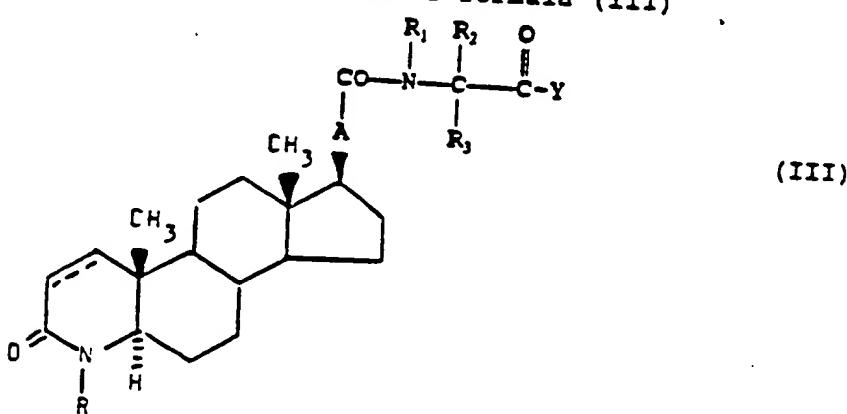
5 1) oxidizing a compound of formula (II)

10



wherein R, R₁, R₂, R₃, A and the symbol are as defined in claim 1 and Z is a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms, so obtaining a compound of formula (I) wherein R, R₁, R₂, R₃, A and the symbol are as defined in claim 1 and Z is a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms; or

15 2) reacting a compound of formula (III)



- 73 -

wherein R, R₁; R₂, R₃, A and the symbol are as defined in claim 1 and Y is OH or an activating group of the carboxylic function with a compound of formula (IV)



5 wherein R₆ and R₇ are as defined in claim 1, so obtaining a compound of formula (I) wherein R, R₁, R₂, R₃, A and the

symbol are as defined in claim 1 and Z is a $-N$

$$\begin{array}{c}
 R_6 \\
 / \\
 \backslash \\
 R_7
 \end{array}$$

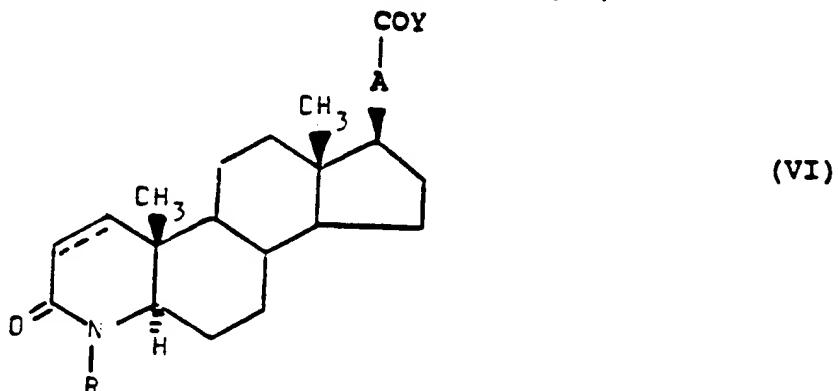
group as defined in claim 1; or

3) reacting a compound of formula (III) as defined
 10 above with a compound of formula (V)



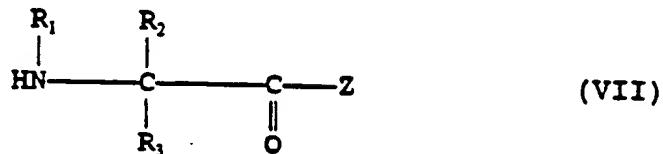
wherein R₈ is a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms and M is a metal atom or a metal-halogen group so obtaining a compound of
 15 formula (I) wherein R, R₁, R₂, R₃, A and the symbol are as defined in claim 1 and Z is a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms,
 or

4) reacting a compound of formula (VI)



- 74 -

wherein R, A and the symbol ... are as defined in claim 1 and Y is OH or an activating group of the carboxy function with a compound of formula (VII)



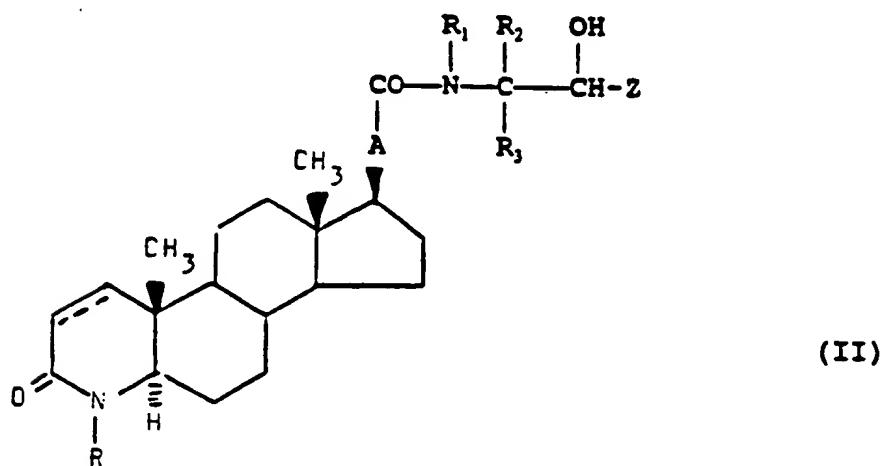
5 wherein R₁, R₂, R₃ and Z are as defined in claim 1, so obtaining a compound of formula (I) wherein R, R₁, R₂, R₃, A, Z and the symbol ... are as defined in claim 1; and, if desired,

5) dehydrogenating a compound of formula (I)

10 wherein R, R₁, R₂, R₃, A and Z are as defined in claim 1 and the symbol ... is a single bond, so obtaining a compound of formula (I) wherein R, R₁, R₂, R₃, A and Z are as defined in claim 1 and the symbol ... is a double bond, and if desired, converting a compound of formula (I) into a

15 pharmaceutically acceptable salt thereof and/or if desired, separating a mixture of isomers of formula (I) into the single isomers.

5. A compound of formula (II):



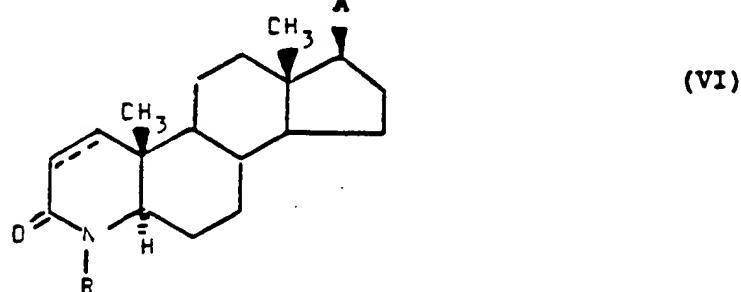
- 75 -

wherein R, R₁, R₂, R₃, A and the symbol are as defined in claim 1 and Z is a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms, with the proviso that at least one of the groups R, R₁, R₂, R₃ and Z contains at least one fluorine atom, and the pharmaceutically acceptable salts thereof.

6. A compound according to claim 5 wherein:
R is hydrogen or methyl;
A is a single bond;
R₁ is hydrogen;
R₂ is methyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl, trifluoromethyl, 1-trifluoromethyleth-1-yl, 2-trifluoromethylprop-1-yl, 2-methylthioeth-1-yl or methoxymethyl, phenyl or benzyl;
R₃ is hydrogen or methyl;
Z is methyl, n-butyl, trifluoromethyl or pentafluoroethyl;
and the symbol ... represents a single or a double bond; provided that at least one of the groups R₂ and Z contains at least one fluorine atom.

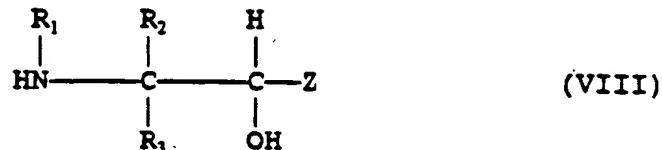
7. A process for the preparation of a compound of formula (II) or a pharmaceutically acceptable salt thereof as defined in claim 5, comprising

(a) reacting a compound of formula (VI)
COY



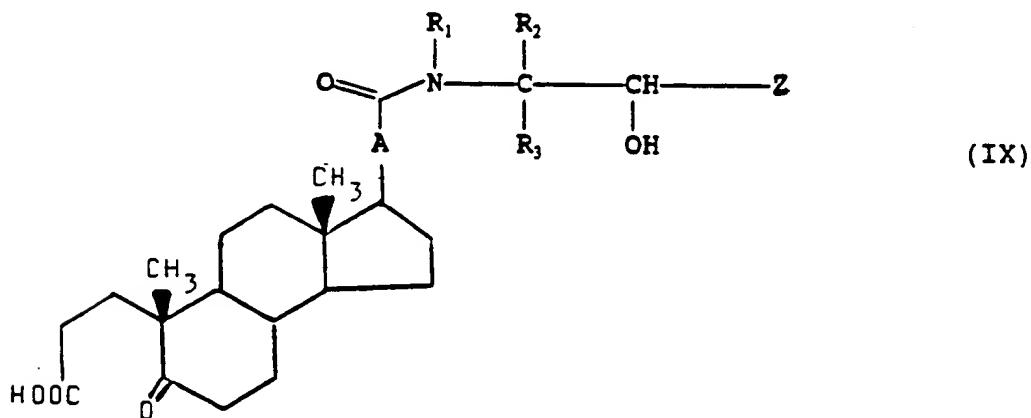
- 76 -

wherein R, A, and the symbol are as defined in claim 5 and Y is OH or an activating group of the carboxy function with a compound of formula (VIII)



5 wherein R₁, R₂ and R₃ are as defined in claim 5 and Z is a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms so obtaining a compound of formula (II) wherein A, R, R₁, R₂, R₃ and the symbol are as defined in claim 5 and Z is a C₁-C₆ alkyl group unsubstituted or
10 substituted by one or more fluorine atoms; or

(b) reacting a compound of formula (IX)

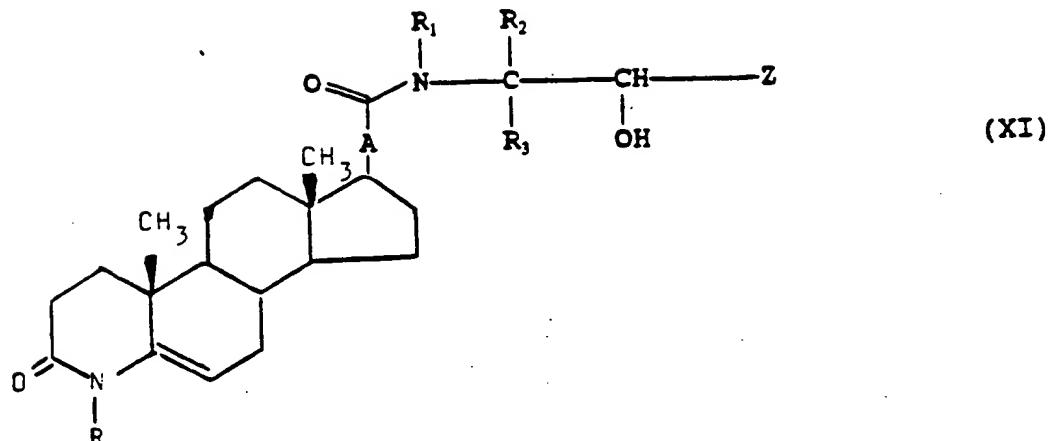


wherein R₁, R₂, R₃ and A are as defined in claim 5 and Z is a C₁-C₆ alkyl group unsubstituted or substituted by one or
15 more fluorine atoms with an amine of formula (X)



wherein R is as defined in claim 5 so obtaining a compound of formula (XI)

- 77 -



wherein A, R, R₁, R₂, and R₃ are as defined in claim 5 and Z is a C₁-C₆ alkyl group unsubstituted or substituted by one or more fluorine atoms, and hydrogenating the compound of formula (XI) so obtaining a compound of formula (II) wherein R, R₁, R₂, R₃ are as defined above, Z is a C₁-C₆ alkyl unsubstituted or substituted by one or more fluorine atoms and the symbol is a single bond.

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and/or diluent and, as an active principle, a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and/or diluent and, as an active principle, a compound of formula (II) as defined in claim 5 or a pharmaceutically acceptable salt thereof.

10. A compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof for use in a method of treatment of the human or animal body by therapy.

20 11. A compound of formula (II) as defined in claim

- 78 -

5 or a pharmaceutically acceptable salt thereof for use in a method of treatment of the human or animal body by therapy.

12. A compound of formula (I) as defined in claim 5, 1, or a pharmaceutically acceptable salt thereof, for use as a testosterone 5 α -reductase inhibitor.

13. A compound of formula (II) as defined in claim 5, or a pharmaceutically acceptable salt thereof, for use as a testosterone 5 α -reductase inhibitor.

10 14. Use of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use as a testosterone 5 α -reductase inhibitor.

15 15. Use of a compound of formula (II) as defined in claim 5 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use as a testosterone 5 α -reductase inhibitor.

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/EP 93/02038

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 5 C07J73/00 A61K31/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 5 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 271 220 (MERCK & CO. INC.) 15 June 1988 see page 8; claims 1,8,9; examples 2,3,6,7,9,10 ---	1,2,4, 8-15
X	EP,A,0 484 094 (SANKYO COMPANY LIMITED) 6 May 1992 see page 2 - page 4; claims 1,28	1,2, 12-15
A	see page 24 - page 27 ---	4,5,7
A	JOURNAL OF MEDICINAL CHEMISTRY vol. 27, no. 12 , 1 December 1984 , WASHINGTON (US) pages 1690 - 1701 G. H. RASMUSSEN ET AL 'Azasteroids as inhibitors of rat prostatic 5-alpha-reductase' see the whole document ---	1,4,5,7, 12
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

- 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- 'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- '&' document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

29 November 1993

20.12.93

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+ 31-70) 340-3016

Authorized officer

Moreno, C

INTERNATIONAL SEARCH REPORT

In ~~total~~ Application No
PCT/EP 93/02038

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF MEDICINAL CHEMISTRY vol. 29, no. 11, 1 November 1986, WASHINGTON, (US) pages 2298 - 2315 G. H. RASMUSSEN ET AL 'Azasteroids: structure-activity relationships for inhibition of 5-alpha-reductase and of androgen receptor binding' see the whole document ---	1,4,5,7, 12
A	EP,A,0 200 859 (FARMITALIA CARLO ERBA S.P.A.) 12 November 1986 see page 1 - page 3; claims ---	1,4,7
A	EP,A,0 155 096 (MERCK & CO. INC.) 18 September 1985 see claims; examples -----	1,7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 93/02038

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0271220	15-06-88	US-A-	4845104	04-07-89
		CA-A-	1284636	04-06-91
		DE-A-	3776520	12-03-92
		JP-A-	63139195	10-06-88
EP-A-0484094	06-05-92	AU-B-	640279	19-08-93
		AU-A-	8682191	30-04-92
		CA-A-	2054368	30-04-92
		CN-A-	1062145	24-06-92
		JP-A-	5032693	09-02-93
EP-A-0200859	12-11-86	JP-A-	61257996	15-11-86
		US-A-	4732897	22-03-88
EP-A-0155096	18-09-85	AU-A-	2748192	18-03-93
		AU-A-	3313589	10-08-89
		AU-B-	584321	25-05-89
		AU-A-	3916785	05-09-85
		AU-A-	7083591	11-07-91
		CA-A-	1314541	16-03-93
		DE-A-	3584172	24-10-91
		EP-A-	0314199	03-05-89
		JP-C-	1518815	29-09-89
		JP-A-	60222497	07-11-85
		JP-B-	63065080	14-12-88
		JP-A-	1093600	12-04-89
		US-A-	4859681	22-08-89
		US-A-	4822803	18-04-89
		US-A-	5049562	17-09-91
		US-A-	5120742	09-06-92
		US-A-	5138063	11-08-92
		US-A-	5151429	29-09-92
		US-A-	4760071	26-07-88

THIS PAGE BLANK (USPTO)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)